The Journal of Laboratory and Clinical Medicine

VOL. V. ST. LOUIS, JULY, 1920 NO. 10

ORIGINAL ARTICLES

LEUKOPLAKIA OF THE PELVIS OF THE KIDNEY—A STUDY IN METAPLASIA*

BY DEWAYNE G. RICHEY, M.D., PITTSBURGH, PA.

THE following study of leukoplakia has been made with more particular reference concerning its development in the pelvis of the kidney as well as offering certain features which suggest some of the underlying factors having to do with the process of metaplasia. We recognize in metaplasia, "the postnatal production of specialized tissues from cells which normally produce tissues of other orders," embracing both a morphologic and functional change in the cells and is an adaptation on the part of the cells to an altered environment. It would appear that this conversion to another form of cell does not occur directly but is brought about only by a preliminary reversion to a vegetative type of cell or, where the mother cells are present, by the development of cells modified by their surroundings. Metaplasia occurs both as a physiologic process and as a result of certain pathologic conditions, the latter involving repeated insults to a tissue over an extended period of time. In either event, the tendency is the formation of more highly specialized tissues from less highly specialized ones, although the reverse may occur. True metaplasia undoubtedly has its limitations, being governed by certain rigid laws and must not be confused with such phenomena as heterotopia, heteroplasia and anaplasia. While tissues of mesoblastic origin lend themselves more readily to metaplastic transformation than those of epiblastic or hypoblastic origin, nevertheless, innumerable examples have been encountered where structures which are normally of the stratified squamous, transitional, cuboidal or columnar type have assumed characteristics of keratinizing stratified squamous epithelium.

Such terms as cornification, keratinization or epidermization which have been applied to metaplasia of epithelial tissues to the stratified squamous character, as

*From the Magee Pathological Institute, Mercy Hospital, Pittsburgh, Pa.
Read before the American Association of Pathologists and Bacteriologists, April, 1920.

a rule, denote a degree of the same process and when the change has become sufficiently prominent to admit of recognition as a pearly, opaque, firm plaque, it is called leukoplakia. Although leukoplakia is more commonly encountered on the tongue and the buccal and esophageal mucous membranes, it is by no means unknown on the surfaces of other viscera and its occurrence along the urinary tract has been noted by several observers. In 1914, Beer collected from the literature forty-five instances of leukoplakia as found along the urinary tract, of which ten occurred in the pelvis of the kidney, supplementing two of his own. To his series can be added those cases described by Rokitanski, Orth, Epstein, Marchand and Pollack.

The present case of leukoplakia occurred in the pelvis of the right kidney which has been removed at operation by Doctor J. J. Buchanan from a man, age 43, who, for twenty-two years, had experienced periodic paroxysms of pain following injury to the back. The seizures would begin high in the right lumbar region and radiate to the genitalia. They would recur two or three times a year, last from several minutes to three hours and were invariably severe. Albumin, pus, blood and mucus were found in the urine from the right kidney. Culture from this urine yielded B. coli communis and B. acidi lactici.

The right kidney weighed 110 grams and was considerably distorted. The lower two-thirds of the kidney was quite healthy, while the upper third of the organ was so cavitated that only a narrow rim of the original renal substance remained. The cavities varied in size from a small marble to a large walnut and communicated freely with the pelvis. A remarkable appearance was noted in connection with the larger cavities at the upper pole. These cavities were lined by a white, silvery, finely wrinkled membrane, looking not unlike the delicately corrugated skin of the scrotum of infants. The surface of the membrane was firm and unbroken, as it extended in fine processes upon the injected walls of the lesser cavities. The pelvis, in the remaining portion of the kidney, showed a similar metaplasia which continued downwards along the tract of the ureter so that it resembled the streaks of leukoplakia seen at the lower end of the esophagus. There was no evidence of calculus or caseation within the organ.

Microscopic section of the kidney substance proper showed some normal portions, and varying stages of obliteration of the glomeruli and tubules by fibrous connective tissue which was, in places, densely infiltrated with lymphoid and plasma cells. Sections taken through the wall of the pelvis and ureter showed the lining to consist of a thick layer of stratified squamous epithelium, presenting a large amount of keratinization on the free surface. The epithelial covering was undulating in character and, though uniform in distribution, was uneven in thickness, varying from ten to eighteen cells in depth. In the intermediate zone, where the cells were polyhedral in shape, definite intercellular bridges were noted, as seen in the prickle cell layer of the epidermis. No membrana propria could be demonstrated, the deepest layer of the epithelium resting directly upon a bed of granulation tissue, into which it exhibited no tendency to invade. The supporting muscle bundles had been extensively fragmented by a replacement fibrosis. The pathologic diagnosis was chronic suppurative pyonephrosis and ureteritis; leukoplakia of pelvis of kidney and ureter.

Metaplasia, as indicated by Orth, entails a transformation of one well-char-

acterized tissue into another equally well-characterized but morphologically and functionally different tissue. Such a conversion occurs through the mediation of cells which are not completely differentiated, so that, as Schridde says, the formative cells of the growing layers of any kind of epithelium, or their immediate daughter cells, may abandon their specific attributes and revert to cells which have all the powers of differentiation possessed by the embyronic cells from which the epithelium developed. Such cells may form any type of epithelium but their power of differentiation is limited to the epithelial tissues and does not include transformation to connective tissue or endothelium. Even Ribbert, the chief antagonist of the theory of metaplasia, in considering the replacement of columnar by squamous epithelium in the submaxillary duct refers to an "innate tend-

Fig. 1.—Leukoplakia of pelvis of kidney.

ency" on the part of this epithelium, a derivative of squamous epithelium to form squamous epithelium and admits the same for like changes in the urinary passages under altered conditions, concluding that only tissues, while externally different, which possess the same histogenic capacities can undergo metaplasia one into another. Consequently with the knowledge that mesothelium may resemble epiblastic derivatives more than other mesoblastic tissue and that the "histogenic capacities" of cells are brought out by their environment, we do not hesitate to explain leukoplakia of the renal pelvis and ureter upon the theory of metaplasia, as a histogenic transformation induced by the alteration of environment wrought by a long-standing inflammatory process with a resultant change in morphology of the cells from the normal transitional to stratified squamous epithelium even to the formation of a superficial layer of keratin, a quality, which

as Wells points out, might be interpreted as an intrinsic chemical alteration in the cells, due to abnormal stimuli.

It will be remembered that the lining of the pelvis and ureter of this kidney had been exposed to chronic inflammation, with repeated losses of the original epithelium, destruction of the basement membrane, and formation of granulation tissue attended by a slowly progressive fibrosis, all of which materially altered the normal biologic conditions of the cells. Haythorn, in studying metaplasia of columnar to stratified squamous epithelium occurring in the bronchus, found that this transformation was present in those places where the basement membrane was absent and we concur with this author that as a result, the mucosa, in its altered surroundings, being destroyed beyond hope of specific regeneration, sought to protect itself with the best reparative cells it could produce in its exhausted state.

The findings in our own laboratories coincide with those reported by Braasch, that, with dilatation of the chronically inflamed pelvis and ureter, limited proliferation and cornification of the mucosa is often seen. Until this process is sufficiently advanced so that it can be recognized in the gross as a definite whitish patch, it is not leukoplakia, but represents only a stage in the process. Although leukoplakia of the renal pelvis and ureter, indicated above, is not rare, it is less common than in the lower urinary passages. It is associated with chronic forms of irritation, as nephrolithiasis and inflammatory processes, either pyogenic or tuberculous. Halle mentions the high coincidence of leukoplakia and calculus, believing, however, that mechanical irritation is not the direct cause, but is secondary to the new conditions arising in chronic inflammation. Just why certain types of mechanical injury or infection do not always cause leukoplakia and why this condition is occasionally, though rarely, observed without the evidence of previous irritation, is, of course, hard to explain. While there is the possibility of some predisposition in the cells of the part, there is also the likelihood of an underlying general disturbance, as the frequent coincidence of syphilis and leukoplakia buccalis in inveterate smokers or of leukoplakia of the esophagus in chronic alcoholics.

In one of the cases reported by Beer and one by Baselin, it was possible to diagnose the condition by the presence in the urine of pearly white membranes, resembling paraffin shavings. In most instances, though, the cholesteatomatous transformation was not suspected until the kidney was examined at operation or necropsy. The clinical manifestations of leukoplakia are usually those of the underlying factor, but the passage of desquamated epithelial plaques has been known to give rise to typical attacks of renal colic. It is reasonable to suspect, in a certain percentage of cases of long-standing pyelitis, which are not amenable to appropriate treatment, that cornification or leukoplakia of the pelvic mucosa has occurred.

That leukoplakia may be the predecessor of carcinoma is indubitable. Osler states that 20 per cent of leukoplakia of the tongue become carcinomatous, while Albarran, Barker, Ewing and others indicate that leukoplakia in any organ should be watched carefully for malignancy, often being, in the absence of early carcinoma, very suspicious of precancerous changes. Morris collected 27 cases of tumors originating in the kidney pelvis, of which 10 were malignant, while re-

cently, Kretschmer was able to gather 43 instances of nonpapillary carcinoma of the renal pelvis, including 21 of apparent transitional or squamous type. The former author states that the most frequent form of carcinoma is transitional or squamous cell, pointing out that long-standing irritation may lead to the transformation of the renal epithelium to an epidermic character, with a resultant leukoplakia which may be the starting point of squamous cell cancer.

In conclusion, therefore, it is clear that leukoplakia of the pelvis of the kidney and ureter is a pathologic entity which seeks logical explanation on the basis of true metaplasia, entailing a transformation from the normal transitional epithelium, even presenting a superficial layer of keratin. It would appear that the absence of a demonstrable membrana propria, as noted by Haythorn, plays an important role in the metaplastic process by permanently altering the environment of the lining cells. The loss of the basement membrane is the outcome of repeated insults wrought by long-continued trauma, either inflammatory, mechanical or both. It is possible that a certain number of cases of pyelitis are refractory to appropriate treatment as a result of leukoplakia of the pelvic mucosa. As in the buccal cavity, bronchi, esophagus, gall bladder, urinary bladder, prostate, fundus uteri and elsewhere, leukoplakia of the renal pelvis and ureter may be a potential site for subsequent malignant metamorphosis.

The author acknowledges his indebtedness to Professor Oskar Klotz for the many valuable suggestions offered during the preparation of this work.

BIBLIOGRAPHY

Adami: Principles of Pathology, 1908, i, 591 and 643.
Adami and McCrae: Textbook of Pathology, 1912, p. 202.
Adami and Nicholls: Principles of Pathology, 1911, ii, 818.
Barker: Practitioner, London, 1914, xciii, ii, 157.
Beer: Am. Jour. Med. Sc., 1914, cxlvii, 244.
Braasch: Jour. Am. Med. Assn., 1919, cxxiii, 733.
Cabot: Modern Urology, 1918, ii, 453.
Ewing: Neoplastic Diseases, 1919, p. 537.
Haythorn: Jour. Med. Research, 1912, xxvi, 523.
Kretschmer: Jour. Urol., 1917, i, 405.
Fuetterer: Lubarsch-Ostertag Ergebnisse, 1903, ii, 715.
MacCallum: Textbook of Pathology, 1919, p. 183.
Morris: System of Medicine (Allbutt and Rolleston), 1908, iv, i, 719.
Osler: Modern Medicine, 1908, v, 66.
Satani: Jour. Urol., 1919, iii, 253.
Wells: Chemical Pathology, 1918, p. 285.
Young and Davis: Jour. Urol., 1917, i, 17.
Ziegler: General Pathology, 1908, p. 314.

CHEMICAL CHANGES IN THE BLOOD IN DISEASE.*

IV. Blood Sugar

By Victor C. Myers, Ph.D., New York City

THAT blood may contain a sugar-like substance was first recognized in 1775 by Dobson, although it was not until seventy years later that its presence in normal blood was discovered by the noted French physiologist, Claude Bernard, who made many of our classic observations on carbohydrate metabolism. By means of his sugar *piqûre* he first noted the connection between hyperglycemia and glycosuria (glycuresis). It remained for Lewis and Benedict[1] in 1913 to introduce a colorimetric method for blood sugar estimation so simple that it could readily be employed for clinical as well as scientific purposes. Earlier in the same year Bang[2] had described a very ingenious method requiring only two to three drops of blood, but the fact that it was a gravimetric-volumetric procedure precluded any very extensive clinical application.

Stimulated by these methods many studies dealing with the sugar of the blood have appeared during the past seven years, while previously to this time Bang[3] had written a very interesting monograph under the title "Der Blutzucker." Obviously reference can be made here only to a few of these papers.**

If we may rely upon the findings with the Benedict method, the blood sugar of the normal human subject falls somewhere between 0.09 and 0.12 per cent, on the average being 0.10 per cent. There are a considerable number of miscellaneous hospital cases, however, which show blood sugars of 0.12 to 0.14 per cent. These figures represent observations made in the morning previous to the intake of any carbohydrate. After a meal rich in carbohydrate there may be an appreciable rise in the sugar content of the blood, while after the intake of even moderately large amounts of glucose, the hyperglycemia may be sufficient to induce a slight temporary glycosuria (glycuresis).†

Conditions of hyperglycemia are much more common and of greater clinical interest than those of hypoglycemia, owing primarily to the fact that diabetes belongs to the former group. Among other conditions which frequently show a moderate hyperglycemia are nephritis and hyperthyroidism. Hypoendocrine function would appear to result in hypoglycemia, and comparatively low blood sugars have been observed in myxedema, cretinism, Addison's disease, pituitary disease and other less clearly defined endocrine conditions such as muscular dystrophy.

*From the Laboratory of Pathological Chemistry, New York Post-Graduate Medical School and Hospital, New York City.

**Among these should be mentioned the papers of Hopkins,[4] Geyelin,[5] Hamman and Hirschman,[6] Denis, Aub and Minot,[7] Mosenthal, Clausen and Hiller,[8] Janney and Isaacson,[9] Bailey,[10] Williams and Humphreys[11] and Allen, Stillman and Fitz.[12]

†As it is now generally recognized that sugar is present in normal urine (to the extent of about 0.05 to 0.20 per cent), the term glycosuria is somewhat of a misnomer. It implies no more than glycemia does in the case of blood. We might speak of a hyperglycosuria in the same way that we refer to a hyperglycemia, or better employ the term "glycuresis" suggested by Benedict.[13] This would indicate an increase in the sugar content of the urine to the extent that it could be detected by *ordinary* qualitative tests, and not a new appearance of sugar.

RELATION OF GLYCOSURIA TO HYPERGLYCEMIA AND THE THRESHOLD POINT

All forms of glycosuria are accompanied by hyperglycemia, if we except the glycosuria produced by such substances as phlorhizin and uranium, and the analogous clinical condition, "renal diabetes." In mild cases of diabetes the hyperglycemia is not excessive, generally 0.2 to 0.3 per cent, although in severe cases figures up to and even above 1.0 per cent have been obtained. The normal threshold of sugar excretion (i.e., the point of glycuresis) is about 0.16 to 0.18 per cent. With blood sugar concentrations of 0.15 to 0.20 per cent the appearance of sugar in the urine is apparently dependent on whether or not diuresis exists, glycosuria appearing especially in the latter case. When the threshold point has been passed, however, the overflow of sugar into the urine may continue until the concentration in the blood has fallen nearly to normal. Mild cases of diabetes usually have a normal threshold, although some severe cases apparently have a lowered threshold, increasing the severity of the condition. Ordinarily in the early stages of the disease there is a fairly direct relationship between the hyperglycemia and glycosuria. In the later stages of the disease, however, cases are frequently encountered with marked hyperglycemia and only slight glycosuria, showing that the threshold point has been raised. The cause of glycosuria in "renal diabetes" is obviously due to the reverse condition, viz., a threshold point below the level of the normal blood sugar.

DIASTATIC ACTIVITY AND HYPERGLYCEMIA

In 1917 Myers and Killian[14] described a simple method of estimating the diastatic activity of the blood and called attention to the fact that conditions of hyperglycemia were associated with an increased diastatic activity, and suggested that this might be the important factor in the production of the hyperglycemia in both diabetes and nephritis. The increase in the diatase of the blood in nephritis finds probable explanation in the decreased excretion of diastase in the urine, now well known in this condition, although a satisfactory explanation of the increased activity in diabetes is not so readily given. De Niord and Schreiner[15] have noted the exception that diabetics who are also syphilitic do not show a high diastatic activity. Table I gives values for blood sugar and diastatic activity in normal individuals, diabetics, nephritics, and illustrative endocrine cases. It will be noted that with the three normals the diastase was 16 and 17 and the blood sugar 0.1 per cent. Cases 4 and 5 are especially interesting, both being physicians whose blood diastase was estimated incidentally to other tests. High diastatic activities being observed, a history of so called "alimentary" glycosuria was elicited in each case. Of the diabetics, Case 7 was on a rigidly restricted diet throughout the period of observation. This serves to explain the comparatively low figures for blood sugar with the high diastase figures, while, on the other hand, the high diastatic activity affords an explanation as to why the restriction in the diet was unable to bring the blood sugar down to normal The improvement in Case 8 was very rapid as is evident by the marked drop which occurred in both the diastatic activity and the sugar in six days. The parallel fluctuations in the diastase and urea in Case 9 would suggest that the increased diastatic activity in nephritis is a retention phenomenon. Hyperfunction on the part of

TABLE I

DIASTATIC ACTIVITY OF THE BLOOD IN NORMAL CASES, DIABETES, NEPHRITIS, ENDOCRINE CONDITIONS AND CARCINOMA OF THE PANCREAS

CASE	AGE	SEX	DIASTATIC ACTIVITY	SUGAR	UREA N	CO_2 COMBINING POWER	REMARKS
				PER CENT	MG. TO 100	C.C. TO 100	
1. J. K.	25	♂	17	0.10	15		
2. A. L.	27	♂	17	0.10	14		Normals
3. R. H.	28	♂	16	0.10	14		
4. E. H.	36	♂	34	0.16	13		Glycosuria noted on one occasion, slight proteinuria.
			29	0.11	12		
5. Z. D.	53	♂	29	0.12	13		Glycosuria noted on two occasions.
6. F. P.	51	♂	74	0.55		54	
			47	0.28			
7. F. M.	26	♂	59	0.17		49	Diabetes, Case 7 being on a rigidly restricted diet during this period.
			44	0.16		56	
			43	0.17			
			39	0.18			
			41	0.20			
8. L. M.	62	♀	42	0.26			
			24	0.12			
9. J. B.	34	♂	32	0.14	60		
			32	0.14	62	32	
			41	0.16	135		
			38	0.16	110		Nephritis
10. J. M.	41	♂	30	0.16	47	47	
11. C. G.	24	♀	24	0.13			Hyperthyroidism
12. J. S.	24	♂	10	0.09	13		Addison's disease
13. T. L.	43	♀	45	0.15			Carcinoma of the pancreas
14. D. M.	63	♂	45	0.14			

the ductless glands appears to result in an increase in the blood diastase and hypofunction in the reverse effect, as shown by the data on Cases 11 and 12.

RENAL DIABETES

So-called "renal diabetes" has been the subject of considerable discussion since Lépine in 1895 postulated the existence of this rather interesting condition in which the glycosuria is actually the result of renal disease, and not due to hyperglycemia as in diabetes. Some thirty cases have now been recorded in the literature, although the condition is probably not as uncommon as this number might imply. A few of these cases have shown definite evidence of renal disease

TABLE II

OBSERVATIONS ON RENAL DIABETES

CASE	AGE	SEX	DATE	SUGAR OF BLOOD	SUGAR OF URINE	REMARKS
				PER CENT	PER CENT	
1. M. B.	31	♀	8/25/15	0.09	1.3	Renal diabetes, diet low in carbohydrate on first test, regular diet on second test.
			10/13/16	0.11	4.5	
2. P. L.	10	♀	5/12/16	0.12	1.2	Cases of parenchymatous nephritis with fairly constant mild glycosuria.
			8/ 7/16	0.14	0.4	
3. J. P.	62	♂	8/27/15	0.18	0.6	
			5/29/16	0.15	1.1	
4. C. M.	54	♂	4/27/15	0.19	1.1	
			12/ 7/15	0.17	0.3	

aside from the glycosuria, but some would appear to be entirely free from the symptoms ordinarily associated with disease of the kidney. Renal diabetes has often been compared with phlorhizin glycosuria, demonstrated by von Mering in 1886, in which condition we have glycosuria without hyperglycemia. Some of the cases, however, appear to find a more direct analogy in the glycosuria of uranium nephritis, in which there is only a mild glycosuria, with a normal or nearly normal glycemia and a constant proteinuria. Data on four cases which might be put in the category of renal diabetes are given in Table II. The first of these was a very typical case of renal diabetes. Bailey[16] has already presented a report of this case (1) and also Case 3 with a general discussion of this subject. The slight glycosuria in the last three cases was associated with parenchymatous nephritis and was quite independent of the mild hyperglycemia found in the last two cases. From the above discussion it is apparent that a satisfactory diagnosis of renal diabetes cannot be made without a knowledge of the blood sugar. Now that this determination may be so easily made it seems probable that many cases presenting a history of a low grade glycosuria but without the classic symptoms of diabetes mellitus, will be definitely recognized as cases of renal diabetes.

DIABETES MELLITUS

Since the glycosuria of diabetes mellitus is dependent upon hyperglycemia, it is apparent that this latter condition is more fundamental than the glycosuria. Glycosuria is evidently only a safety factor, and the internist in applying his dietetic treatment should endeavor primarily to relieve the hyperglycemia; although in so doing he relieves the glycosuria, he should be finally guided by the concentration of sugar in the blood. In the early stages of the disease the glycosuria is an excellent index of the hyperglycemia, but when the threshold point has been raised, as for example in diabetes associated with chronic kidney disease, the disappearance of sugar in the urine is a rather poor guide to the glycemia. As will be observed in Table III, blood sugar figures of 0.2 to 0.3 per cent, and

TABLE III

INFLUENCE OF NEPHRITIS UPON THE EXCRETION OF SUGAR IN DIABETES

CASE	AGE	SEX	SUGAR	OF	SEVERITY OF NEPHRITIS	CASE	AGE	SEX	SUGAR	OF	SEVERITY OF NEPHRITIS
			BLOOD	URINE					BLOOD	URINE	
			PER CENT	PER CENT					PER CENT	PER CENT	
1	63	♀	0.19	0	++	11	53	♂	0.37	1.7	++
2	47	♂	0.22	0	++	12	35	♀	0.38	6.2	?
3	53	♂	0.24	1.7	+	13	48	♀	0.39	2.2	++
4	57	♀	0.24	5.0	++	14	30	♂	0.42	5.0	?
5	27	♀	0.31	6.0	+	15	46	♀	0.42	3.6	+++
6	61	♀	0.33	0.5	++	16	50	♀	0.46	0	+++
7	61	♂	0.34	6.3	+	17	56	♀	0.57	8.0	+
8	68	♂	0.35	0	+++	18	15	♂	0.79	8.7	+
9	23	♀	0.36	7.0	—	19	53	♂	0.98	1.6	++
10	47	♂	0.36	1.2	+++	20	52	♀	1.10	0.5	++

Data obtained previous to beginning treatment; taken from Myers and Bailey.

even more, may be noted without the appearance of any sugar in the urine. Although some cases with definite nephritic symptoms retain the power of secreting a urine of high sugar content, severe nephritis appears to reduce markedly

the permeability of the kidney for sugar; and it is only when these latter cases are excluded from the above table that there appears to be any relation between the hyperglycemia and glycosuria. Although this table probably gives an exaggerated impression of the occurrence of nephritis in diabetes, since the cases were those needing hospital care, it is not believed that the importance of this subject has been fully appreciated, although previously discussed by the older workers.[3, 18] Fitz[19] has presented evidence to show that impaired renal function exists in many cases of advanced diabetes. Williams and Humphreys[11] have made a study of the blood sugar threshold in diabetes and have observed in general that as age advances, the threshold rises. In connection with treatment they state: "Our experience has lead us to the conclusion that it is desirable to maintain the blood sugar level as nearly normal as possible even though severe restrictions in diet may be necessary for the purpose, notwithstanding the fact that in most cases the high threshold will permit of a much more liberal diet without the appearance of sugar in the urine." In discussing the high blood sugars which are observed in some diabetics on a protein-fat diet, Mosenthal[8] has suggested that this may merely be a protective measure to adjust carbohydrate metabolism for the more advantageous utilization of glucose.

It is worthy of note in this connection that several interesting contributions dealing with the action of certain salts on the permeability of the kidney for sugar and the sugar threshold have come from Hamburger's[20] laboratory.

NEPHRITIS

It has been recognized for some time that many cases of severe nephritis show high figures for blood sugar. We have presented several papers giving such data,[14, 17] while Williams and Humphreys have made this subject the topic of a special paper.[11] They found that the range of the blood sugar levels was from 0.08 to 0.25 per cent, varying directly with the severity of the disease.

TABLE IV

BLOOD SUGAR OBSERVATIONS IN SEVERE NEPHRITIS

CASE	AGE	SEX	DATE	SUGAR	CREATININE	UREA N
				PER CENT	MG. TO 100 C.C.	MG. TO 100 C.C.
1. E. M.	39	♂	12/ 4/15	0.225	21.5	129
			12/ 7/15	0.180	21.8	129
2. J. B.	34	♂	1/26/17	0.195	8.2	53
			2/23/17	0.114	7.9	61
			2/27/17	0.120	7.5	45
			3/ 2/17	0.117	6.6	44
3. F. F.	8	♂	12/18/17	0.106	6.1	106
			12/21/17	0.150	5.9	93
4. A. N.	27	♀	3/11/18	0.181	8.6	97
			3/19/18	0.131	9.4	102
			3/22/18	0.120	12.6	110
			3/26/18	0.161	12.1	110
5. M. D.	30	♀	5/27/20	0.121	6.5	42
			6/ 1/20	0.121	5.5	43
6. F. M.	57	♀	6/ 3/20	0.153	4.8	59
			6/18/20	0.096	3.5	43
7. A. D.	66	♀	6/ 5/20	0.163	2.8	30
8. M. I.	75	♀	6/16/20	0.172	7.0	121
			6/21/20	0.190	5.7	147

Hamman and Hirschman[6] have studied the sugar tolerance in nephritis and state that in many cases there is a profound change in carbohydrate metabolism, the blood sugar curve after the ingestion of glucose resembling the "diabetic curve." When there is marked interference with renal function very small amounts of sugar or none appear in the urine, although the blood sugar may go above 0.2 per cent. Bailey[10] has presented data on a very interesting case of nephritis where the blood sugar rose to 0.3 per cent before a slight glycosuria occurred. No satisfactory explanation of the hyperglycemia has been offered, although the suggestion has been made that some disturbance in the adrenals or other endocrine glands may be responsible for both the high blood pressure and the increased blood sugar. As already noted Myers and Killian[14] have observed an increased diastatic activity of the blood in this condition. Hyperglycemia data in nephritis are given in Tables I and IV. It should perhaps be noted here that Morgulis and Jahr[21] have criticized the findings of high blood sugars in nephritis on the basis of error due to interference of creatinine in the sugar estimation. While there is no doubt that the creatinine does influence some of the blood sugar findings, the error is much less than they imply and does not invalidate the deductions that have been made. This criticism has been further discussed in connection with the method below.

ENDOCRINE CONDITIONS

That cases of hyperthyroidism frequently show high blood sugars (although not often in the fasting state), and that alimentary glycosuria may be readily provoked in this condition has been recognized for some time. Blood sugar observations obtained after glucose tolerance tests have given us much more definite information regarding the carbohydrate tolerance of individuals with endocrine disorders than the older studies made on the urine. Experimental

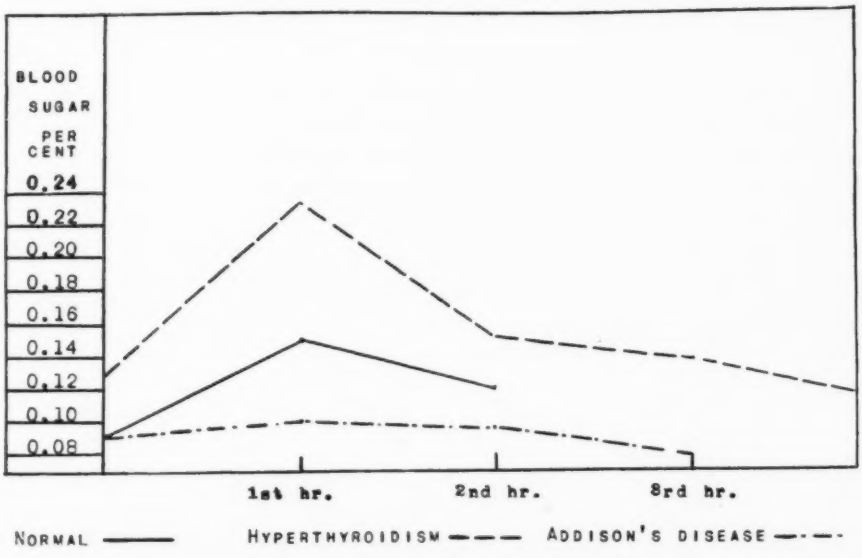


Chart 1.—Illustrative glucose tolerance tests.

proof that hypoglycemia results from hypo-endocrine function was obtained by Janney and Isaacson[9] in the case of the thyroid, where hypoglycemia regularly developed after thyroidectomy. Low blood sugar values, figures ranging from 0.06 to 0.09 per cent, have been reported in myxedema,[5] cretinism,[9] Addison's disease, pituitary disease and other less clearly defined conditions such as muscular dystrophy. The last mentioned condition has been discussed by Janney, Goodhart and Isaacson[22] and McCrudden and Sargent.[23] Altogether twelve cases were reported, the blood sugars ranging from 0.064 to 0.086.

CARBOHYDRATE TOLERANCE TESTS

The advent of a simple method for blood sugar has made possible the estimation of the blood sugar concentration at short intervals after the administration of carbohydrate, usually glucose. With this method of study it has been possible to obtain much more consistent data regarding the carbohydrate tolerance than with similar tests formerly carried out on the urine, chiefly for the reason that the threshold point of renal excretion is not here a factor in the test. This test has served to put many of our older views, especially those regarding glucose tolerance in endocrine conditions, on a more firm foundation. A number of the papers to which reference has already been made present data obtained with this method of study. The papers of Hamman and Hirschman,[6] and Williams and Humphreys[11] nicely demonstrate the great value of this method particularly in cases of diabetes and nephritis. Bailey[10] has presented quite extensive data on a few cases covering a wide variety of conditions and emphasizes the value of obtaining blood specimens at quarter hour intervals during the first hour and at half hour intervals thereafter until the sugar concentration returns to normal. With this technic the character of the curve is very clearly brought out. In practical work, however, this large number of determinations is not always possible. As a rule four sugar estimations at one hour intervals will serve to show the type of curve, despite the fact that the highest point in the curve may frequently be missed.

The method employed in this laboratory by Killian[24] is as follows: The patient is given, the first thing in the morning, a standard breakfast consisting of two slices of bread, one egg in any form and one cup of water. Two hours after this breakfast the patient empties the bladder and then receives 200 c.c. of water to drink. One hour after this a specimen of blood and a specimen of urine are taken to serve as controls. The patient then takes glucose, 1.75 grams per kilo of body weight in 50 per cent solution. Specimens of blood are now taken every hour for three to four hours, the sugar determined as described below and a curve plotted. Following the taking of glucose a 24-hour specimen of urine is collected and the glucose determined with the Benedict methods, by titration if the amount is large, otherwise by the colorimetric method.[25]

It is not possible in the compass of the present paper to describe in detail the characteristics of the different types of curves obtained, although an idea of the curves observed in hyper-and hypo-endocrine conditions may be obtained from Chart I. This chart presents unpublished observations of Killian, showing a severe case of hyperthyroidism and a case of Addison's disease contrasted with a normal.

ESTIMATION OF BLOOD SUGAR

A large number of methods have been described for the estimation of blood sugar. Although many of these methods determine the reducing power of the blood (presumably in large part glucose) with a high degree of accuracy, and have given us considerable insight into this phase of carbohydrate metabolism; nevertheless, most of them have been so technical as to require special equipment and training, and are therefore not suited to clinical purposes. S. R. Benedict, who introduced the most satisfactory tests we possess for sugar in urine, has performed, in collaboration with Lewis,[1] a similar service for the sugar of the blood. The general principle and technic of this method are far simpler than those of any other method, and for this reason it is particularly well suited to clinical purposes. The method is dependent upon the fact that very small amounts of glucose react with picric acid and sodium carbonate to produce a red color (sodium picramate). In the actual test the picric acid serves the additional purpose of precipitating the proteins of the blood. As has been pointed out by Myers and Bailey,[17] the technic of Lewis and Benedict may be considerably simplified by a lower dilution of the blood, so that the direct picric acid filtrate may at once be used for the colorimetric estimation without evaporation. This method is the one described below.

There has recently been so much discussion of blood sugar methods that some remarks should be made regarding four other methods, which have recently been introduced, and also regarding certain criticisms which have been made of the picric acid method. Höst and Hatlehol[26] have just presented some very interesting comparative data on the methods of (1) Bang and Hatlehol[27] (Bang's most recent method), of (2) Hagedorn and Jensen,[28] of the (3) Myers-Bailey modification[17] of the Lewis-Benedict method and of the method of (4) Folin and Wu.[29] (The other of the four methods referred to above is the new titration method of McLean.[30]) Höst and Hatlehol find that the first two methods which are titrimetric agree quite closely, but give somewhat lower results than the second two which are colorimetric. This is true of the diabetic bloods in particular, the picric acid method giving the highest results. It is worthy of note that the duplicate determinations with this method were particularly satisfactory. While these differences are theoretically very interesting and will probably be suitably explained, they are so small as to possess no clinical significance in themselves.

Höst and Hatlehol have given the technic of the method of Hagedorn and Jensen which is very neat and requires only 0.1 c.c. of blood. The method of Folin and Wu is adapted to their tungstic acid blood filtrate and requires the equivalent of 0.2 c.c. of blood. Although this method gives results which are slightly lower than with the Benedict method, it is probably subject to somewhat the same sources of error. It nicely fits their scheme of blood analysis but as an individual determination it requires more time and attention than the picric acid method. They have recently introduced certain improvements.[31]

A year ago Morgulis and Jahr[21] offered certain criticisms of the Lewis-Benedict method, directed especially to the influence of creatinine. They stated: "It is probable, therefore, that the Lewis-Benedict method is applicable to normal bloods when the creatinine concentration is about 1 to 3 mg. per 100 c.c., but

under pathologic conditions when the creatinine level may rise to 10 to 40 mg. per 100 c.c., the sugar analysis by the Lewis-Benedict method loses its value as a quantitative procedure." Criticism was made of results obtained with either the original Lewis-Benedict method or our modification of it, although Morgulis and Jahr employed Benedict's new picric acid sodium picrate reagent,[32] this being much more sensitive to creatinine than the picric acid alone, owing to the

TABLE V

INFLUENCE OF CREATININE ON THE ACCURACY OF THE BLOOD SUGAR ESTIMATION

GLUCOSE PLUS CREATININE	PICRIC ACID REAGENT					PICRIC ACID-SODIUM PICRATE REAGENT
	READINGS MADE AT ONCE	SUGAR FOUND	READINGS MADE NEXT DAY	SUGAR FOUND	READINGS CALCULATED	SUGAR FOUND
MG. TO 100 C.C.	MM.	MG.	MM.	MG.	MM.	MG.
1. 100 + 5	14	107	14.5	104	14.3	113
2. 100 + 10	13	115	13.4	112	13.6	122
3. 100 + 20	12	125	12.7	118	12.5	150

The colorimetric readings made at once (as soon as the solution had cooled), were made roughly. Since the sodium picramate color formed from glucose does not appreciably fade, we frequently make these readings on the next day. These second readings were made with considerable care. Readings calculated on the basis of the same color development for creatinine as sugar agree very well with these figures. The readings in the case of the sodium picrate reagent were taken on two days with little change in the values.

presence of hydroxide. In their experiments they found that creatinine gave 3 to 5 times as much color as glucose. In our first paper[33] on the subject in 1915 we stated: "It is well to remember, especially in uremia, that each mg. of creatinine present in the blood introduces an error of approximately the same magnitude in per cent," i.e., gives the same amount of color as glucose. This is borne out by the data in the table above. For example, a blood showing 20 mg. creatinine would raise a blood sugar from 0.100 to 0.120 per cent. It is perfectly apparent that this would not account for blood sugars of from 0.15 to 0.25 per cent. In six years we have encountered only 10 cases with over 20 mg. creatinine, and only one of these exceeded 30 mg. out of about 125 cases having over 5 mg. creatinine. In view of the fact that creatinines as high as 20 mg., to say nothing of 40 mg., are seldom found, and also the findings given in Tables IV and V, it is apparent that creatinine does not invalidate the findings of hyperglycemia in nephritis, at least when the method below is employed. In this particular, Benedict's most recent blood sugar method would appear to be more subject to error from creatinine than his original method or our modification of it, but as Benedict[25] has recently pointed out in connection with the estimation of the sugar content of normal urine, it is perfectly possible to completely remove the creatinine and other interfering substances with charcoal or completely dissipate the color derived from the creatinine with the aid of acetone.

Method[17].—To 8 c.c. of distilled water in a 20 c.c. cylindrical centrifuge tube are added 2 c.c. of the well-mixed oxalated blood (or oxalated plasma). This is then stirred with a glass rod until the blood is thoroughly hemolyzed, after which about 0.5 grams of dry picric acid (sufficient to completely precipitate the proteins and render the solution saturated) is added. The mixture is thoroughly stirred at intervals of several minutes until it is uniformly yellow, after which it is centrifuged and the supernatant liquid filtered into a dry test tube through a small 4 cm. filter paper. (As indicated in the preceding paper on creatinine, the

sugar estimation may be combined with the creatinine, both estimations being carried out on portions of the same picric acid filtrate.)

Three c.c. of filtrate are pipetted into a tall, narrow test tube 12 x 200 mm., (sugar tube) graduated to 3, 4, 10, 15 and 20 c.c., 1 c.c. of saturated (22 per cent) sodium carbonate is added, and the tube heated in a beaker of boiling water for 15 to 20 minutes. Simultaneously 3 c.c. of a 0.02 per cent solution of glucose in saturated picric acid (keeps permanently) is treated with a similar amount of sodium carbonate in a sugar tube and heated at the same time as the unknown. This serves as the standard. Under the action of the heat and alkali the yellow sodium picrate is converted to reddish-brown sodium picramate in proportion to the amount of sugar present. The solutions are now cooled to room temperature either by allowing the tubes to stand or by placing them in a beaker of water. The solution in the standard tube is made up to exactly 10 c.c. with water employing a pipette, preferably with a rubber bulb, so as not to overrun the mark. The unknown tube is now diluted to 10, 15 or 20 c.c., (or some other definite volume in a graduated cylinder) that approximates the color of the standard. It is best to allow a little time to elapse before color comparisons are made.

The standard may conveniently be set at the 15 mm. mark on the colorimeter (Bock-Benedict, Kober or Duboscq). Since the 3 c.c. of blood filtrate employed are the equivalent of 0.6 c.c. of blood and the 3 c.c. of standard solution contain 0.6 mg. of glucose, the proportions are the same as though 100 c.c. of blood and 0.1 gram of glucose were employed. For the calculation the following formula may be used:

$$\frac{S \times D \times 0.1}{R \times 10} = \text{blood sugar in per cent,}$$

in which "S" represents the depth of the standard (15 mm.), "D" the dilution of the unknown, 0.1 the strength of the standard in grams, calculated on the basis of 100 c.c of blood, "R" the reading of the unknown and 10 the dilution of the standard.

ESTIMATION OF BLOOD SUGAR WITH THE TEST TUBE COLORIMETER

The test tube colorimeter is particularly well adapted to the blood sugar determinations.

Method.—For the blood sugar estimation one may use 3 c.c. of the same filtrate as employed for the creatinine estimation (see preceding paper). If only the sugar is desired the following technic may be used: 2 c.c. of the well-mixed oxalated blood are treated with 8 c.c. of water (4 volumes) in a 20 c.c. cylindrical centrifuge tube. After the corpuscles have been laked, about 0.5 gm. of dry picric acid is added and the mixture stirred at intervals with a glass rod until it is a light yellow. When the protein precipitation is complete, the tube is centrifuged and the supernatant fluid filtered through a small filter paper.

Three c.c. of the filtrate are now pipetted into a test tube (or the right-hand tube of the colorimeter) and 1 c.c. of saturated sodium carbonate (22 per cent) added. To another test tube (or the left hand tube of the colorimeter) add 3 c.c. of 0.02 per cent glucose solution in saturated picric acid (standard) and 1 c.c. of the saturated sodium carbonate. The tubes are now placed in a beaker of boiling water for 15 to 20 minutes, then removed and allowed to cool. The standard is made up to the 10 c.c. mark in the left hand tube with water. The unknown is diluted with water with the aid of the diluting pipette, inverting after each addition, until identical in color with the standard. Since the equivalent of 0.6 c.c. of blood is employed and 0.6 mg. of glucose is used as a standard, the proportion is the same as though 100 c.c. of blood were used and 0.1 gram of glucose. This being the case, the reading in the unknown tube gives the percentage of blood sugar directly, i.e., a reading of 9 c.c. being equivalent to 0.09 per cent sugar, a reading of 25 c.c. per cent, etc.

ESTIMATION OF THE DIASTATIC ACTIVITY OF THE BLOOD

As indicated above, the diastatic activity of the blood may often furnish information not disclosed by the blood sugar alone. For this reason directions are given for the determination.

Method[14].—Two 2 c.c. samples of oxalated blood are taken, one being employed as a control. The control tube* is made up to 10 c.c. with distilled water, and the tube to be employed for the test to 9 c.c. Both tubes (20 c.c. cylindrical centrifuge tubes) are now placed in a water bath arranged to maintain a constant temperature of 40° C. As soon as the contents of the tube have been brought to this temperature, 1 c.c. of 1 per cent soluble starch† (or glycogen) is added to the second tube, the contents are mixed, and the incubation carried out for exactly 15 minutes at 40° C. After the incubation has been completed, about 0.5 gram of dry picric acid is at once added to each tube and the mixtures are stirred. When the proteins are precipitated, the tubes are centrifuged and the yellow supernatant fluid is filtered. The sugar in 3 c.c. portions of the filtrate is now estimated as described above for the blood sugar. Correction is made for the sugar originally present in the blood (with the aid of the control) and for the slight reducing action of the soluble starch, if any exists. It has seemed most convenient to record the results in terms of the percentage of the soluble starch (10 mg.) transformed to reducing sugars (calculated as glucose) by the 2 c.c. of blood employed.

The following formula may be used for the calculation of the reducing sugar content of the control (C) and test (A) specimen $\frac{S \times D \times 2.0}{R \times 10}$ = mg. of reducing sugar in terms of glucose for 2 c.c. of blood, in which "S" represents the depth of the standard (15 mm.), "D" the dilution of the unknown in c.c., 2.0 the strength of the standard in mg. compared to 2 c.c. of blood, "R" the reading of the unknown in mm. and 10 the dilution of the standard. The difference between the results of the control and test specimens times 10 gives the percentage transformation of the starch to reducing sugar (diastatic activity), provided the soluble starch requires no correction. For example, a diabetic blood having 0.26 per cent blood sugar would give a control of 5.2 mg. Suppose the test specimen gave 9.8 mg. reducing sugar and the soluble starch contained 6 per cent reducing substance, 9.8 – (5.2 + 0.6) times 10 would give a diastatic activity of 40.

REFERENCES

[1]Lewis and Benedict: Proc. Soc. Exper. Biol. and Med., 1913, xi, 57; Jour Biol. Chem., 1915, xx, 61.
[2]Bang: Biochem. Zeitschr., 1913, lvii, 300.
[3]Bang: Der Blutzucker, Wiesbaden, 1913.
[4]Hopkins: Am. Jour. Med. Sc., 1915, cxlix, 254.
[5]Geyelin: Arch. Int. Med., 1915, xv, 975.
[6]Hamman and Hirschman: Arch. Int. Med., 1917, xx, 761.
[7]Denis, Aub and Minot: Arch. Int. Med., 1917, xx, 964.
[8]Mosenthal, Clausen and Hiller: Arch. Int. Med., 1918, xxi, 93.
[9]Janney and Isaacson: Arch. Int. Med., 1918, xxii, 160.
[10]Bailey: Arch. Int. Med., 1919, xxiii, 455.
[11]Williams and Humphreys: Arch. Int. Med., 1919, xxiii, 537, 546, 559.
[12]Allen, Stillman and Fitz: Monographs of the Rockefeller Institute for Medical Research, No. 11, 1919, (October).
[13]Benedict, Osterberg and Neuwirth: Jour. Biol. Chem., 1918, xxxiv, 258.
[14]Myers and Killian: Jour. Biol. Chem., 1917, xxix, 179.
[15]DeNiord and Schreiner: Arch. Int. Med., 1919, xxiii, 484.
[16]Bailey: Am. Jour. Med. Sc., 1919, clvii, 221.
[17]Myers and Bailey: Jour. Biol. Chem., 1916, xxiv, 147.

*If a sugar estimation is being made simultaneously, there appears to be no good reason for running a control, since a 15 minutes' incubation results in no very appreciable change in the blood sugar. The control may, however, be made the basis of the blood sugar estimation.

†Many preparations of soluble starch on the market contain reducing sugar. Starch containing much in excess of 6 per cent reducing sugar is not suitable for this work. For some time we have employed soluble starch prepared by the method of Small[34] from potato starch. This is practically free from reducing sugar. Glycogen is free from reducing sugar and theoretically is to be preferred. Practically, good *soluble starch* gives the same results and is much less expensive.

[18]von Noorden: Metabolism and Practical Medicine, English Ed., 1907, iii, 529.
[19]Fitz: Arch. Int. Med., 1917, xx, 809.
[20]Hamburger: Brit. Med. Jour., 1919, i, 267.
[21]Morgulis and Jahr: Jour. Biol. Chem., 1919, xxxix, 119.
[22]Janney, Goodhart and Isaacson: Arch. Int. Med., 1918, xxi, 188.
[23]McCrudden and Sargent: Arch. Int. Med., 1918, xxi, 252.
[24]Killian: Proc. Soc. Exper. Biol. and Med., 1920, xvii, (Feb.).
[25]Benedict: Proc. Soc. Exper. Biol. and Med., 1920, xvii, (May).
[26]Höst and Hatlehol: Jour. Biol. Chem., 1920, xlii, 347.
[27]Bang and Hatlehol: Biochem. Zeitschr., 1918, lxxxvii, 264.
[28]Hagedorn and Jensen: Ugesk. Læger, 1918, lxxx, 1217.
[29]Folin and Wu: Jour. Biol. Chem., 1919, xxxviii, 81.
[30]MacLean: Biochem. Jour., 1919, xiii.
[31]Folin and Wu: Jour. Biol. Chem., 1920, xli, 367.
[32]Benedict: Jour. Biol. Chem., 1918, xxxiv, 203.
[33]Myers: Chemical Composition of the Blood, 1915, p. 29.
[34]Small: Jour. Am. Chem. Soc., 1919, xli, 113.

BACILLUS INFLUENZÆ IN NORMAL AND PATHOLOGIC THROATS*

By Lloyd Arnold, M.D., Nashville, Tenn.

THE Bacillus influenzæ (Pfeiffer) has been studied with renewed vigor during the past two years. It was considered as an etiologic factor in the acute respiratory disease which was pandemic in 1918, by many observers. In view of the difference of opinion that now exists on this point, it was thought advisable to make a few observations in this locality on the prevalence of B. influenzæ in average normal throats, in cases of acute rhinitis, and in throats of patients suffering from "influenza"—which was epidemic in Nashville in February, 1920.

HISTORICAL

Pringle and Huxham in 1743 named a disease, which they thought was due to the influence of atmospheric conditions—sudden changes—influxus, or influenza. Pfeiffer[28] was the first to find a microorganism that could be regarded as the cause of this condition. He found just after the 1889-92 pandemic, a short, small, gram-negative bacillus, aerobic, hemophilic, reaching maximum growth in about 24 hours at 37° C., no growth occurring at temperature below 28° C. nor above 42° C.

Wassermann[41] in 1893 believed that if Pfeiffer's bacillus was found in a throat, this individual suffered from influenza, and that it was never found in healthy individuals, and was always associated with influenza.

Kretz[16] in 1897, found the B. influenzæ in throats of patients several months after an attack of influenza. This author named such individuals "Influenza carriers."

Ortner[25] in 1903, believed that influenza was always caused by Pfeiffer's bacillus, but it could under some conditions be demonstrated in patients not suffering from influenza. This worker called attention to the fact that influenza had never entirely disappeared from Europe since the pandemic of 1889-90, but had been endemic ever since, and that cases had occurred in the region of Vienna every winter and spring since that time.

Rosenthal[33] in 1900 and 1903, found B. influenzæ in the larynx and trachea in about 20 per cent of all healthy persons examined; from this he concluded that this was a saprophyte, and not a pathogenic form.

The B. influenzæ had a rather wide distribution in this country previous to the pandemic in 1918. Lord[20, 21] in 1902 found it in pure culture in 30 per cent of the cases of nontuberculous lung infections in this period. Holt[12] in 1910 found it in 63 per cent of acute bronchitis or pneumonia during the winter and spring in New York City. This author also records that 23.2 per cent of 185 cases, not suspected—patients and nurses—were carriers of B. influenzæ. Woll-

*From the City Hospital Laboratory, Nashville, Tenn.

stein[40] in 1906 found this organism in many nontuberculous lesions of the respiratory tract in children in New York.

Hastings and Niles[11] in the period from 1903 to 1911, found this bacillus in the upper respiratory tract in many pathological conditions.

Luetscher[19] in 1915, at the Johns Hopkins Hospital found, in his studies on some 600 cases of nontuberculous infections of the respiratory tract the pneumococcus and B. influenzæ as the cause of 91 per cent of the infections of the bronchi and lungs; of these B. influenzæ alone in about 30 per cent; in infections of larynx 20 per cent, and in infections of the head 13 per cent. During the pandemic of 1918 the B. influenzæ has been demonstrated in the sputum, nasal secretions, and in nasopharynx in a high percentage of cases where proper methods have been used. In England McIntosh,[23] Fildes and Thompson,[8] Mathews,[22] Eyre and Lowe,[7] and others found it in the majority of cases examined. In Germany, Papamarku,[30] Levinthan,[17] Hundeshagen,[13] and others.

Some work has been done in this country on the number of carriers of this organism. Lord, Scott and Nye[18] found in 34 healthy Harvard S. A. T. C. recruits, 76 per cent carriers of B. influenzæ.

Opie and coworkers[24] found 35.1 per cent Pfeiffer's bacillus in the mouths of healthy men examined at Camp Funston.

Park and Williams[26] found 40 per cent of nurses carriers of B. influenzæ, also that 41 per cent of patients not suffering from respiratory troubles admitted to wards were positive. Pritchett and Stillman[29] found 43 per cent of normal individuals examined to be carriers.

Winchell and Stillman[38] found 40 to 46 per cent of 100 normal individuals examined monthly from December, 1918, to June, 1919, were carriers. They found from a comparison with studies carried on previous to the pandemic, that there were no more carriers during the epidemic period than there were previously.

Wahl, White and Lyall[37] found that B. influenzæ when experimentally implanted in the nares of healthy men disappeared in 24 to 72 hours, but multiplication took place rapidly and remained for a considerable length of time, two weeks or more, when in the nasopharynx, and was very resistant to disinfectants.

Wollstein[39] found two general morphologic forms of B. influenzæ, a short and a long type. Cultural strains are of the short type, meningeal strains belong to the long type, but these become shorter on artificial cultural medium. This author considers the moisture present in the cultural medium has a great influence on the morphology. Many workers have substantiated these findings. The author has noticed these characteristics repeatedly. There has also been found on continuous transplants a long filamentous looking form, which we took for contamination. It resembles certain fungi morphologically. Wade and Manalang[36]have studied this form and consider it a form of B. influenzæ.

Park[27] tested by agglutinin absorption about 100 strains of B. influenzæ and found that the strains isolated from the same case give the same immunologic reactions, but seldom occurred with strains from different individuals. Park concludes, "that influenzæ bacillus, like the pneumococci, have gradually through the years altered on the mucous membranes of healthy carriers into many strains which, while having many characteristics in common, are still different in their susceptibility to specific immune substances and perhaps other

reactions." Park found that one colony from a plate culture made from several strains may show two different strains immunologically, but separated when thoroughly shaken up before plating.

Many workers have shown that B. influenzæ was capable of producing variable amounts of toxins. Huntoon and Hannum[14] showed that certain conditions of symbiotic growth intensified the liberation of the toxin. Roos[32] found that the symbiosis of streptococci and B. influenzæ increased the virulency of the latter tenfold. This was first observed by Jacobson.[15]

METHODS OF ISOLATION OF BACILLUS INFLUENZÆ

1. *Hemophilic Property Alone.*—Blood agar plates. Pfeiffer found pigeons blood more advantageous than human's blood. Davis found that in mediums containing as little as 1:180,000 of hemoglobin the organism may continue to grow. Czaplowski[5a] found the organism grew better when very small amounts of blood were added to the medium, hardly enough to tint, than when large quantities were added. Ghon and Preyss[10a] found that hemoglobin in smaller amounts than was demonstrable with the spectroscope was sufficient to promote growth.

Rivers[31] found rabbits' and cats' blood produced better growth than human blood. Fitzgerald and Cohen[9] obtained good growths by heating the blood to 80° C. for three minutes. Mathews[22] showed a very profuse growth occurs when blood has been digested with an excess of trypsin for 5 days at 37° C. Fleming[10] recommends treatment of blood with acid and neutralizing with alkali, this medium giving a simple and good differential medium.

2. Symbiotic Relationship for Growth.—Cantani[4] showed the favorable influence of other organisms upon the growth of B. influenzæ on artificial mediums. Organisms now used are B. subtilis, staphylococci, streptococci. Roos,[32] Brown and Orcutt[3a] both have developed differential methods in this manner.

3. Special Differential Mediums.—Bernstein and Lowe[3] used Churchman's observation that gentian-violet inhibited growth of gram-positive organisms. These authors have used this dye in concentration of 1:5000 in blood agar plates. Avery[1] after considerable experimentation used sodium oleate in 1:1000 concentration in blood agar plates, serum-free blood being used. Winchell and Stillman,[38] using Avery's method, found that the best results were obtained when the P_H of the medium was between 7.2 and 7.5.

TECHNIC

Avery's sodium oleate method was used, great care being taken in the adjustment of the P_H value. This latter was the most important point in the success of the method. The Barnett and Chapman[2] colorimetric method was used. Swabs were taken from the posterior nasopharynx and immediately smeared across a poured and surface dried Avery Sodium Oleate Blood Agar Plate, being distributed by means of a bent glass spreader. Plates were inverted and incubated forty-eight hours. It was found that the colonies were better developed and as contamination and spreaders were few, this was more satisfactory than a shorter incubation period. Colonies looking like B. influenzæ were picked, stained by Gram method and tested for hemophilic property.

EXPERIMENTAL

October, 1919, to January, 1920, 80 apparently normal throats were examined by this method, 28 were positive, making 35 per cent carriers of B. influenzæ.

In November, 1919, there occurred a slight epidemic of acute pharyngitis and rhinitis in this locality. Of 45 such cases that were examined, 35 were positive, making 77.7 per cent positive.

In February, 1920, there was a recurrence of the "influenza" epidemic in this locality, lasting some two weeks. During this time 104 cases were selected at random from the patients entering the hospital, diagnosed as "influenza" in the acute stage. Many of these cases had been sick several days before admission. Of the 104 cases, 90 were positive, making 87.5 per cent positive.

EXPERIMENTS ON THE VIABILITY OF BACILLUS INFLUENZÆ

Nasal secretions, known by cultural methods to contain B. influenzæ, were taken up with cotton swabs.

No. 1 swab left at room temperature for 4 hours. Culture positive.
" 2 swab left at room temperature for 6 hours. Culture positive.
" 3 swab left at room temperature for 8 hours. Culture positive—one colony.
" 4 swab left at room temperature for 10 hours. Culture negative.
" 5 swab left at room temperature for 12 hours. Culture negative.

Room temperature was 22.5° C. day time, but no sun light.

Nasal secretions, known by cultural methods to contain B. influenzæ, were taken up on sterile gauze, placed under a bell-jar on a glass plate, at room temperature.

No. 1 Culture made after 6 hours. Positive.
" 2 Culture made after 12 hours. Positive.
" 3 Culture made after 18 hours. Positive—few colonies.
" 4 Culture made after 24 hours. Positive—one colony.
" 5 Culture made after 36 hours. Negative.
" 6 Culture made after 48 hours. Negative.

DISCUSSION

It would seem that the percentage of carriers of B. influenzæ (35 per cent) is about the same in Nashville as in New York, Boston, Camp Funston, and elsewhere. Stillman states that the carriers were not numerically increased during the recent pandemic of influenza. Lyall found when B. influenzæ were planted on the nasopharynx they were very resistant to antiseptics and remained for weeks. Stillman found some 84 individuals constant carriers of Pfeiffer's bacillus, over a period of seven months. In cases of acute rhinitis and pharyngitis, we found 77.7 per cent of 45 cases, all occurring within the hospital during a period of ten days, were positive to B. influenzæ. In February, 1920, during the recurrence of the influenza epidemic in Nashville, of the 104 cases run 87.5 per cent were positive to Pfeiffer's bacillus.

A percentage of 87.5 during the apex of an epidemic was lower than was expected to be found, especially since acute upper respiratory disorders gave

77.7 per cent. The same media and the same technic were used for both observations. In a subsequent paper on the throat flora previous and during this February, 1920, epidemic of influenza, this question will be dealt with in detail.

CONCLUSIONS

Bacillus influenzæ is present in 35 per cent of normal throats in this vicinity.

Bacillus influenzæ was present in 77.7 per cent of "bad colds"—acute rhinitis and pharyngitis.

Bacillus influenzæ was present in 86.5 per cent of the cases in the recent—February, 1920—epidemic of influenza in Nashville.

Bacillus influenzæ, in nasal secretions from acute rhinitis, directly exposed to the air, are not viable if planted on artificial culture medium after 10 hours; if exposed to light, but desiccation prevented, are viable for 24 hours.

With Avery's sodium oleate blood agar plates, we have a reliable method of isolating the B. influenzæ.

REFERENCES

[1]Avery: Jour. Am. Med. Assn., 1918, lxxi, 2050.
[2]Barnett and Chapman: Ibid., 1918, lxx, 1062.
[3]Bernstein and Lowe: Jour. Infect. Dis., 1919, xxiv, 129.
[3a]Brown and Orcutt: Jour. Exper. Med., 1918, xxviii, 659.
[4]Cantani: Zeitschr. f. Hyg., 1901, xxx, 29.
[5]Crowe and Thacker-Neville: Bull. Johns Hopkins Hosp., 1919, xxx, 322.
[5a]Czaplowski: Centralbl. f. Bakteriol., I.O., 1902, xxxii, 667.
[6]Davis: Jour. Infect. Dis., 1907, iv, 73.
[7]Eyre and Lowe: Lancet, London, Oct. 12, 1918.
[8]Fildes and Thompson: Lancet, London, 1918, ii, 699.
[9]Fitzgerald and Cohen: Centralbl. f. Bakteriol., 1911.
[10]Fleming: Lancet, London, 1919, i, 139.
[10a]Ghon and Preyss: Centralbl. f. Bakteriol., 1902, xxxii, 96.
[11]Hastings and Niles: Jour. Exper. Med., 1911, xiii, 639.
[12]Holt: Arch. Int. Med., 1910, v, 449.
[13]Hundeshagen: Deutsch. med. Wchnschr., 1918, xliv, 1181.
[14]Huntoon and Hannum: Jour. Immunol., 1919, iv, 167.
[15]Jacobson: Arch. de med. exper., 1900, xiii, 425.
[16]Kretz: Wien. klin. Wchnschr., 1897, x, 877.
[17]Levinthal: Berl. klin. Wchnschr., 1918, lv, 712; Ztschr., f. Hyg. u. Infektk., 1918, lxxxvi, No. 1.
[18]Lord, Scott, and Nye: Jour. Am. Med. Assn., 1919, lxxii, 188.
[19]Luetscher: Arch. Int. Med., 1915, xvi, 657.
[20]Lord: Boston Med. and Surg. Jour., 1902, cxlvii, 662.
[21]Lord: Ibid., 1905, clii, 574.
[22]Mathews: Lancet, London, July 27, 1918.
[23]McIntosh: Lancet, London, 1918, ii, 695.
[24]Opie, et al: Jour. Am. Med. Assn., 1919, lxxii, 108.
[25]Ortner: Deutsch. Klin., 1903, ii, 417.
[26]Park and Williams: Am. Jour. Pub. Health, 1919, ix, 45.
[27]Park: Jour. Am. Med. Assn., 1919, lxxiii, 318.
[28]Pfeiffer: Deutsch. med. Wchnschr., 1892, xviii, 28; Ztschr. f. Hyg., 1893, xii, 357.
[29]Pritchett and Stillman: Jour. Exper. Med., 1919, xxix, 259.
[30]Papamarku: Deutsch. med. Wchnschr., October 24, 1918.
[31]Rivers: Bull. Johns Hopkins Hosp., 1919, xxx, 129.
[32]Roos: Jour. Immunol., 1919, iv, 189.
[33]Rosenthal: Comp. rend. Soc. d. Biol., 1900, liii, 266.
[34]Rosenthal: Ibid., 1903, lv, 1500.
[35]Wade and Manalang: Jour. Exper. Med., 1920, xxxi, 95.
[37]Wahl, White and Lyall: Jour. Infect. Dis., 1919, xxv, 419.
[38]Winchell and Stillman: Jour. Exper. Med., 1919, xxx, 497.
[39]Wollstein: Jour. Exper. Med., 1915, xxii, 445.
[40]Wollstein: Ibid., 1906, viii, 681.
[41]Wassermann: Deutsch. med. Wchnschr., 1893, xix, 1201.

THE LOCALIZATION OF HALLUCINATIONS*

By H. I. Gosline, M.D., Howard, Rhode Island

IN THE consideration of localization of any sort, is it not a desirable condition if not an essential one, that we know the ground in which our localization is to take place? That we do not know our ground any too well when we consider the central nervous system, I take to be almost axiomatic. Necessarily, much of the evidence upon which our conception of the structure of the central nervous system is built, is in the nature of indirect evidence. It has proved utterly impossible to trace nerve fibers from start to finish. However, with the uncertain tools of indirect evidence neuropathology has succeeded in building up a fair conception of the structure of the centripetal pathways, the centrifugal pathways and to a certain extent the arrival platforms for sensations and the departure platforms for motion.

That there must, at least logically, be a connection between the sensory arrival platforms and the motor departure platforms seems rarely to have concerned the anatomists. Under the spell of old forms of psychology they have preferred to look for association tracts and centers for abstract ideas or concrete ideas. Flechsig thought he had found the association tracts in the brains of his fetus;[1] Campbell thought he had found the centers for concepts and for concrete ideas in the so-called silent areas of the brain.[2] But, strangely enough, the discovery does not seem to have led very far, or to have suggested any new lines of advance. So far, it has proved barren from a practical standpoint.

In lieu of better histopathologic methods which seem rather slow in coming, it occurred to the writer that one might more easily attack the problem from the psychologic side. This side seemed especially hopeful for several reasons. First, there were some aspects that had been neglected even from the point of view of elementary logic. I have named one aspect above in the connection which I mentioned as necessarily existing logically between the arrival and the departure platforms. Another ran as follows: How do you expect to correlate symptoms with anatomy until you are sure that your symptoms are indivisible? In other words that they are elementary? The thought also must have arisen somehow that most any one could propound psychology of some of the ancient sort.

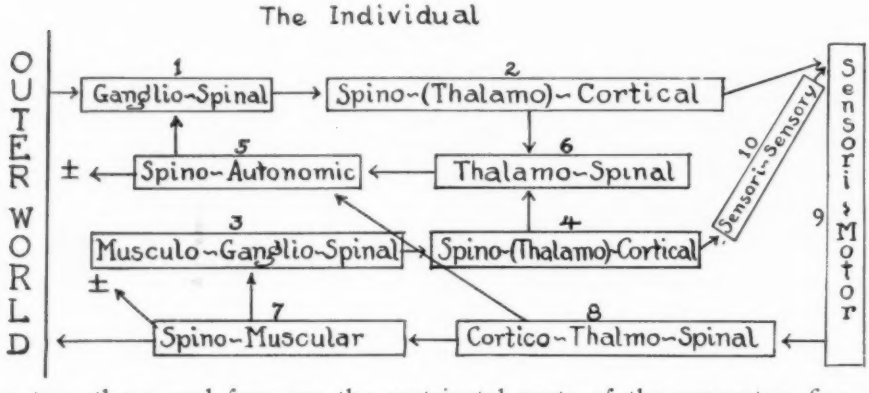
However, a thorough search revealed that it was not necessary to propound any psychology of an ancient sort but that with the institution of laboratory methods, a psychology had already grown up which might offer some outlook.[3] That psychology seems to have reduced all mental processes to four simple or elementary processes, sensation, association, reaction and inhibition, and it is these processes that can be correlated with our anatomy. Strangely enough, a

*From the Department of Pathology, State Institutions, Howard, Rhode Island.
Read at the meeting of the New England Psychiatric Society, held at the Danvers State Hospital, March 25, 1920.

set of logical deductions from this psychology made lucid the structure of the gray matter of the cortex as well as that of the white matter of the brain.

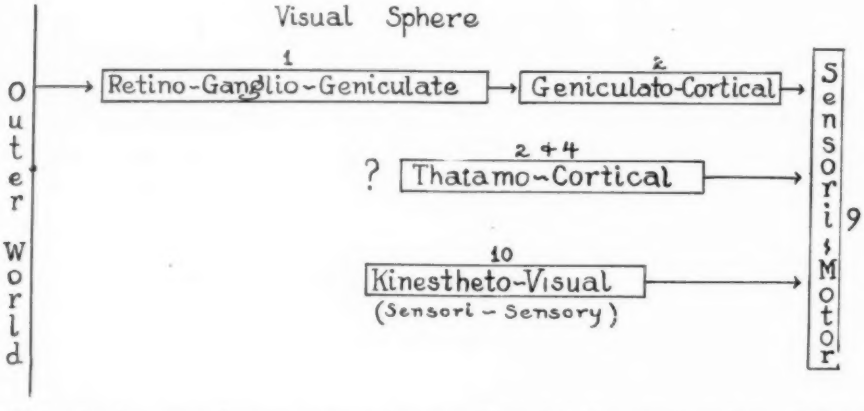
Before proceeding to the structure deduced from this psychology let me emphasize the fact, if it requires any emphasis, that this set of plans of the central nervous system is only a logical deduction, has not been proved anatomically and is so new as not to have been put to the pragmatic test. However, I will ask your forbearance, while I inflict it upon you, assuring you that a thorough search of both the psychologic and anatomic literature has failed to reveal one iota against it and has actually revealed a great deal for it by a mere mental recasting of some of the facts as we have known them for many years.

Following is the paradigm of the central and peripheral nervous system:



One, two, three, and four are the centripetal parts of the apparatus, five, six, seven, and eight are the centrifugal parts and nine and ten are the connecting parts deduced from the psychology we mentioned.

The detail of the visual system is then as follows:



This single example can serve as a paradigm for the construction of the rest of the nervous system, for anyone who is interested enough to take the time and trouble.

Let us leave the anatomic field for the moment and recall to your memories some axioms relating to function. May it not be assumed that the following thesis is axiomatic? Sensations depend upon the structure and function of the

peripheral and central apparatus and upon the condition of the consciousness. If the structure is so altered as to be that of the dead substance, it may be assumed that the function will be completely lost. That is apparently not the state of the nerve structure in the case of hallucinations, for function is retained and in fact some of the structures are functioning without apparent stimulus. One would scarcely suppose a paralysis of function in a case where function was taking place without adequate cause. One would more logically assume an overactivity. The question of whether the overfunction is due to irritation by direct involvement of the paths concerned or by removal of the effects of other paths is an extremely attractive one. It has previously been presented to you under the title of "Hyperkinesis by Defect"[4] and I feel that our newer psychology bears this assumption out. Common examples of this condition are known to you all. The exaggeration of the reflexes when the spinal reflex arc is retained and the inhibitory control of the corticospinal tracts is removed, is used by all of you daily in the phenomenon of the patella reflex. I am assuming for the purposes of this paper that the same phenomenon is universal in the nervous system; that, in other words, there is a mutual inhibition of neurones which seek a final common path[5] and that this phenomenon is born in the nerve tissue, is a function of nerve tissue, is part of the machinery of our bodies. Naturally, I am not denying at the same time that changes in the blood supply, poisons, et cetera may cause conditions of excitation in the paths concerned or that exciting conditions in the sense organs may play a part, if only to act as points of departure for excitations. But what I do wish to emphasize is the state of irritability in the sense centres as against a defect in the sense centres and that the irritability may be due not only to direct contact with irritating conditions but also to the removal of the inhibitions of neurones seeking a final common path through the sensory centre.

Referring again to our diagrams, you can see anatomically for yourselves how an injury of the spinocortical neurone or of the thalmocortical neurone may allow the one or the other to overact thus overstimulating the sensorimotor neurone. The defect, the pathologic anatomy is not to be expected or looked for then in the sensorimotor neurone but in the spinocortical or the thalamocortical neurone. We are not to expect changes in the cerebral cortex in this case but in the subcortical white matter.

Let us make the attempt to localize from the symptoms presented by our patients. We can omit for the purposes of this paper the absent function in the blind or the deaf as well as the artificial performance of function under the electric current. We might also do well to omit the hallucinations which are to a certain extent dependent upon pathologic conditions in the external apparatus. In this group we may consider the unilateral visual hallucinations which do not show hemiopic limitation, hallucinations that may be made to disappear by covering one eye, those which move with the movements of the eyes, which may be doubled by prisms or by lateral pressure on the orbit, or that may appear larger or smaller by looking through an opera glass, or that may appear in the mirror. Cases of a similar sort have not been reported in the other senses.

The following sources of hallucinations are psychologically possible, adhering to the laboratory type of psychology which has been worked out within

the last twenty-five years. The sensations, the associations, the reactions and inhibitions may be disordered. These are the only possibilities. Naturally, these disorders are not revealed immediately to the senses of the observer but appear to him in the form of disordered perceptions, disordered ideas, disordered activities. disordered inner states. The personality, consisting as it does in an intricate interplay of these complex mental functions, is disintegrated in direct proportion to the disintegration in these complex functions. By an analysis which I cannot present at this time, but which can be found in print in the near future and which can be made by yourselves from the proper sources, all these complex mental functions are reduced to the simple processes sensation, association, reaction and inhibition.[6] The specific sensations involved in any given case must be determined from the productions of the patient. So also the specific localization must be derived in every case from the productions of the patient. It is the purpose of this paper to point out in general the simple functions involved in the common hallucinations of our patients.

Let us consider the visual sphere first.

Only a few of the symptoms as we find them may be directly correlated with our anatomy as presented in the charts. Even the simplest objects of visual hallucinations such as the seeing of patterns, flowers, animals reveal the elements of size and shape and we know from our psychology that these are given to our consciousness by the sensations which arise from the action of the eye muscles. May it not be then, that a disorder of the kinesthetic centre for the eye muscles will produce a visual hallucination of varying size, shape and position? The only essential is that the sensorisensory neurone be disturbed from the kinesthetic centre for eye muscle movements to the arrival platform for visual sensations. Perhaps the presence of size, shape and position is evidence of the intactness of that sensorisensory neurone and it is the sizeless, shapeless, and positionless hallucinations that mean a destruction of the sensorisensory neurone. Of the same nature are the hallucinations of birds flying behind one, of a knife seen behind one, of being able to look from behind into ones own body. Nocturnal visions of radiant figures belong here as do the seeing of coins, wire, woven threads or the active, gay crowds of the alcoholic. Of the same nature are the microscopic visual hallucinations of the cocaine addict, the countless similar, tiny individuals, animals, holes in the wall and little points that they see.

Naturally, in some of the examples mentioned you will see another complex mental function, the emotions or the feelings, appear. Patterns appear beautiful to some and hence have an esthetic value. Flowers and animals frequently have emotional equivalents. May not fear be at the bottom of the hallucination of a knife behind one? But the emotions themselves as well as the esthetic attitude are given to our consciousness through our reactions. To remove or to overstimulate the pathways from our emotional centers to our visual arrival platforms may then cause visual hallucinations by the process of excitation or that of hyperkinesis by defect.

Turning to the auditory sphere we may assume that the process of hyperkinesis by defect is working in the case of hallucinations whose content is meaningless words, repeated over and over. But in this case the defect is in the functions which give meaning to the words. Our psychology analyzes the

perception of meaning into reaction. That is to say, our reaction to an object of perception, to an idea which stands for an object of perception is the thing which gives the perception or the idea its meaning; it is the reaction to a combination of sensations which unifies them into a perception and which gives the perception its meaning. In the example of hallucination just given, then, the defect is in the reactive mechanism or in its sensory arrival platforms or in connections between the sensory arrival platforms for the reaction sensations and the sensory arrival platform for the auditory sensations.

Alcoholics can at times hear the buzzing of a fly ostensibly held in the hand placed at their ear. The attention is directed toward the hearing of an imaginary sound. The attention is a function of the reaction mechanism. The discharge of the reaction mechanism and its sensory results are in this case able to stimulate the sensory mechanism for audition. The same is true for the hearing of imaginary telephone conversations by the alcoholic. The localization is to be expected and looked for in the reaction mechanism or in the sensory arrival platforms for the reaction mechanism or in the sensorisensory neurone connecting these arrival platforms with the arrival platform for the auditory sense.

The combination with the muscle sense which gives the space perception seems to exist in the case of auditory hallucinations as well as in that of the visual hallucinations. Of this sort are the voices that are placed in the abdomen, breast, head, ears, in the wall, or in the bed in which the patient lies.

On the other hand, the localization may be entirely in the sensory arrival platform for the auditory sense, that is, in the sensorimotor neurone in the case of hallucinations of different pitch, of different tone coloring, in the soft, whispering, faint, or the loud, piercing hallucinations, or in the short broken remarks, the loud shouting, the crackling, or the bell-tone hallucinations. Do we not see the peculiar features of audition itself in the pitch and tone-coloring? Is not soft, whispering faint or loud and piercing merely differences of intensity which are not peculiar to anything but audition itself? Even remarks, shouting and crackling are combinations of tones and noises, the two categories which comprise all sounds to which the human machine is sensitive.

In the case of a patient whose hallucinations are different in the two ears, it would be necessary to analyze in the same way. It might happen that the same elements were effective in each side or that they were different. In case they differed we should expect to find the lesion in different loci in the two sides of the brain.

The presence of a speech defect should lead one to consider the possibility of a single lesion producing the two disorders, that is to say, the speech defect and the auditory hallucinations. In the brain the two pathways lie very close together in the white matter.

In the case of hallucinations of smell, one might think as we did with those of sight and sound, of a lesion in the sensory arrival platform for smell, if the smell is always the same and often repeated, without other concomitant phenomena to lead us to look elsewhere.

The localization is to be determined as pointed out above in the case of a patient who describes objects ostensibly placed in the closed hand but not really placed there. The disorder is in the attention. The irritation of an overacting

reaction mechanism influences the arrival platform for the tactile sense and causes it to react with an hallucination.

Disorders of the kinesthetic senses may be seen in the following examples and may be submitted to the same processes of analysis for the purpose of localization. The chief ones are feelings of stiffness, of change in the skin or soft parts, of being filled up, sewed up, drawn in, feelings of electricity, of metamorphosis, of inner petrifaction, of drying up, of loss of the head, mouth, stomach. The feeling of being possessed may have an emotional background and the feeling that words are spoken by others in the patient's own tongue seem to point directly to localization in the arrival platform for the sensations from the muscles of the tongue.

In the individual case the analysis is aided by other observations on the patients. Symptoms never occur singly and the final localization is to be made from the analysis of all the symptoms. For example in the cases of hallucination already cited, some patients cut off all other stimuli in order to follow the hallucinations, others produce lively sensations in order to get rid of the hallucinations, while still others stop up the ears, making it appear that outside noises increase the native irritability of the central arrival platforms. Some hallucinations are worse at night or in the loneliness of the prison cell. In these cases the attention and the emotions should be analyzed. In other words the localization should be thought of in the reaction mechanism.

Some cases of hallucination apparently occur by the process of association. In the analysis of the association process it comes out that no new paths are involved and least of all paths connecting all sense arrival platforms directly with one another as we have always assumed till now. All associations take place by contiguity or by similarity. The first means that they must occur together or in immediate succession and the second means that they must have sufficient elements in common to give the feeling of similarity. In other words similarity is a function of the reaction mechanisms. We also know that things are associated in the mind if they have occurred recently, frequently, are emotionally important or are impressive, that is to say, if they have some attention value. Recency and frequency are matters of time and repetition. Emotion and attention values might make us suppose that there are connections between the sensory arrival platforms and the centres for emotions on the one hand and the reactions on the other. We have already been led to make this conclusion previously from other considerations. It is by the process of association that the normal person presents himself the visual picture of the cat whose mee-owing he hears. So we can enumerate the seeing of colors with the hearing of certain sounds, the pain at seeing others suffering pain, the feeling in the larynx when hearing a hoarse singer, the tickling at the suggestion of being tickled, the warding off a blow. Dreams also make a transfer of the senses. The original sense equipment plays a part in some of these cases, depending on whether the individual concerned ordinarily and habitually used visual, auditory or kinesthetic imagery, in other words, depending on his inborn mechanism.

In the case of hallucinations by association in the visual sphere we have the hearing of tones from a tuning fork or from a hand organ which produce visual hallucinations. A glance or a movement may produce peculiar feelings of ten-

sion or of restfulness in some patients. A case is presented where a deaf, blind boy heard bells playing a melody when he moved his eyes in rhythm toward the right. Auditory hallucinations have been produced by stroking different parts of the body. From our presentation above we do not need to consider recency, frequency or contiguity. In the first instance, the hallucinations may be due to these very things or they may be produced by the fact that the emotional reaction to the sounds was similar to that produced by the vision. The disorder in his case would not be true hallucination though practically impossible to differentiate from one. It would be more in the nature of a feeling that the visual impression took place than a real visual impression such as occurs in a true hallucination. In the second case, the visual impression produces a muscle sensation. The balance may be taken to be disturbed in the emotional control, in the thalamocortical neurone. In the third case, the overstimulation of the sensory arrival platform for audition from the sensory arrival platform for muscle sensations is apparent. In the fourth case we have an instance similar to the first one but the part functioning is the tactile sphere.

The analysis is not always given directly from the hallucinations but light may be thrown upon the processes at fault from other fields. Ideas may all be grouped under memory, imaginative and general ideas. There are no ideas which may not be grouped in one of these three groups. And the ideas can be reduced to sensations, association, reaction and inhibition. In this way several disorders which are somehow related to hallucinations and which are sometimes difficult to distinguish from them in practice, are of use to the analyst. In the disorder known as "double thinking" the "thoughts come out loud." A word thought of is heard spoken outside or as a sort of inner speaking. "Inner voices" are not hallucinations, either; they are like the voice of conscience, between hearing and having a presentiment. To these inner voices belong the suggestions, the world speech, thoughts, telephoning and telegraphing. They may attach themselves to another person and a silent dialogue ensues.

In cases where it is impossible to give the content verbatim, we are more likely concerned with convincing thoughts than with true hallucinations. These thoughts are ascribed to strange influences, are often considered supernatural. God or Christ gives the patient a charge or a promise, explains to him a secret of his personality. These phenomena appear dreamy and transcendental to the patient.

While these are not true hallucinations and so will not take our time for analysis here, is it not apparent that practically the same factors are at work in them as have already been outlined in the analysis of the true hallucinations? And, since these same phenomena together with others appear in the hallucinated patient, is it not apparent that the one aids in limiting the analysis of the other to certain ultimate and definite neurone systems? It is these phenomena which have led some to say that hallucinations may be imaginative ideas of extreme sensory vividness and which have led other authors to speak of imaginative hallucinations, psychic hallucinations, pseudo-hallucinations and apperception hallucinations.

Some hallucinations can be influenced by forms of will tension. They may disappear with work and return with leisure. An inhibition of thinking and will

may be at the bottom of these cases. The hallucinations may be independent of the will and of the train of thought, giving the feeling that they are strange, independent, come from the outside. Thus their subjective origin is hidden from the patient. But a psychological analysis of will, attention and thought itself shows that the fundamental disorder in these cases is in the reaction mechanism plus the ideas and the ideas are reduced to the processes of sensation, association, reaction and inhibition.

The last group of complex mental functions that may act in the causation of hallucinations is that of the inner states which comprise the feelings, the emotions and the attitudes. This group offers the chief difficulties to analysis both because it comes into the majority of all hallucinations and because the reaction mechanisms upon which it depends for its existence are so complicated. The reaction mechanisms concerned in the emotions apparently involve the vegetative nervous system and the glands of internal secretion as well as some of the glands provided with a duct. It is apparent then, that we have gone about as far as we can at the present time and in the present state of our knowledge if we are able to say that the disorder is probably in the vascular-glandular system rather than in the central nervous system, in a given case. We have gone still further if we can say that it is probably in the nature of an irritative lesion or of a destructive lesion with hyperginesis by defect as the essential process at bottom of the condition.

The attempt will be made to present all hallucinations in accordance with the latter viewpoint and in some cases to classify them more exactly under the former category.

We know that hallucinations often agree with the thoughts, fears and wishes of the patient and for this reason they seem to be so powerful. The emotional undercurrents in the form of secret hopes and dim longings stand out, causing the absence of perception of real stimuli, a sort of negative hallucination which occurs in the hysteric. In such cases, also, the hallucination or disorder is frequently in a single sense. It is not due to lack of attention, failing attention, or distracted attention. It is not due to clouding of consciousness, to disorder of the sense organ or to disorder of conduction to the brain. The simplest, commonest way of describing it without committing oneself is to call it psychogenic.

The attempt in this paper is made to further analyze "psychogenic" and necessarily commits one to certain views although they are only logical ones.

The following hallucinations are taken to have an emotional background and hence, on the basis of our diagrams, we must assume a hyperkinesis of the thalamocortical neurone by defect of the sensorisensory neurone or an overaction of the thalamocortical neurone from some other cause. This other cause may lie in the vegetative nervous system or the glands of internal secretion. In the hysteric we have already mentioned absence of function of the blindness, the deafness, the absence of the sense of touch or anesthesia. Hallucinations of a single sense, whether of sight, sound, taste, smell, touch, or of general sensibility are to be thought of as hysterical in origin. In such patients the neglect of one side of a bilateral visual hallucination will present to the observer as a unilateral visual hallucination. Hysterics also see veiled forms, dead relatives, men with long knives.

In the visual sphere the following hallucinations show a strong emotional factor: the nocturnal "visions" of God, Christ, the angels, the dead, flowers, fearful faces, the devil, shadow plays, wild animals; the alcoholic hallucinations of rats, goblins, numberless creeping vermin, butterflies, birds, black dogs, wolves, looking in at the window, on the bed covers, dark shadows, blood, the face of a corpse, men hanging from a tree; the epileptic hallucinations of seeing fire, frightful forms, heavenly visions.

In the auditory sphere the same is true of the hearing of the voices of relatives, faithless lovers, hateful neighbors, God, the devil; hearing confused crying, pleasing music and singing. The epileptic hears threats, shooting, war-crys, promises, and angel music. The circular depressions hear single short remarks of a disquieting content. Some schizophrenics hear exciting, gladdening voices at first.

Some patients taste unappetizing, harmful things, such as human flesh in the mouth, dirt, arsenic, cantharides given them by their enemies. They smell poisonous vapors which are made to kill them and the odor of sulphur which comes from the devil.

The common assumption in all these cases is that the abuse, the insults, the jeers, the cries of abused relatives, the threats, the commands only excite, torment the patient and make him suspicious, dangerous, anxious, confused, or make him run away and do senseless, unnatural acts. On the contrary may it not be that these hallucinations only echo the woes of the patient? It is the woes of the patient that color his visual, his auditory, his tactile, his olfactory, his gustatory, his thermic, his algesic, and his kinesthetic hallucinations. On the basis of the James-Lange theory[7] of emotion and of the action theory of introspective psychology is it not more likely that the reaction mechanism is disordered than that the sensations are disordered and are upsetting the reaction mechanism? It is on the basis that this is a correct assumption that I would have you look in these cases for pathology in the sensorisensory neurone of a destructive sort or for pathology in the thalamocortical neurone of an irritative sort, or for pathology in the glands of internal secretion or in the controlling nervous mechanism of the vegetative nervous system.

The fear reaction may have its basis in a disorder of the chromaffine system but farther than this we cannot go at the present time with any degree of certainty.

A few examples of hallucinations colored by removal of the emotional control and consequent overaction of the sensorisensory neurone have been cited above in the paragraphs on the origin of the hallucinations in the sense centers. To these may be added the indifferent, senseless auditory hallucinations of some cases of dementia precox or the case of a patient who slaps her abdomen because she is hard inside and takes douches because she is black inside.

Another group of productions of great assistance to the analyst is that of the illusions or those productions in which an illusion is mixed in with an hallucination so inextricably that it is impossible to tell where one begins and the other leaves off practically. For the purposes of this sort of analysis a separation into hallucinations and illusions lacks point because more information is gathered and more light is cast on the localization by leaving them together. However,

the determination of an illusion is at times of value in pointing to an irritation in the external apparatus or in the first sensory neurone, the ganglio-spinal neurone. Such cases are those caused by the endogenous retinal light or the endotic noises. Others in the visual sphere are conditioned and determined to a certain extent by uneven lights as in the case of alcoholics who read off words and numbers from a clear sheet, or by specks on a smoothe surface on which the alcoholic sees animals. In these cases also, in the delirious state, hallucinations can be produced by pressing on the eyes.

In the auditory sphere the beat of the carotid pulse is at times the apparent cause of rhythmic hallucinations. Soft noises like the dripping of water or the sighing of the wind may cause the hallucinations. In the tactile sphere hallucinations can be produced in some alcoholics by pressing on the skin.

In the following example perhaps it is the attention that is disordered. The patient says that pictures shown to him hide real objects or only let the real objects shimmer through.

In the following examples the memory and the attention both seem to be affected. The patient recognizes relatives in strangers or does not recognize his own relatives as such.

The attention has already been analyzed. The memory renews previous perceptions and hence the analysis of the perceptions involved should lead to the proper localization.

The following mixtures of illusion and hallucination have an emotional background and their analysis should proceed on the same plan as that of the hallucinations themselves. And in making the final estimate of the localization in any given case, these should certainly be used for the valuable aid that they give in fixing the localization of the cause of the true hallucinations. In the visual sphere, towering tree-tops and scurrying mists are specters to the patient. When eating, he sees moulds in his food and little heads cut off with moving eyes, and he sees wiggling worms. Objects about are distortions, skulls; they move and change themselves; people change faces and forms and make faces at the patients.

In the auditory sphere, but still conditioned by the emotions, we may group the following examples: the idea of danger from water produced by roaring and ringing in the ears; the ringing of bells, the scratching of a pen, the whistling of an engine, the barking of a dog, the creaking of a wagon or of some boards may be insulting words or reproaches against the patient; noises mean the crying of the patient's children, crackling means the fires of hell; behind his back words refer to him, remarks accompany his every action and openly expose the most hidden occurrence of his past; the voices insult, threaten, bless, especially if indistinctly heard; wagons creak and rumble in an unusual way and tell stories; swine grunt names and give wonderful attestations; dogs insult and bark reproaches; hens cackle them; geese and ducks quack names, phrases and fragments of references.

Most of the examples above, if not all, give evidence of the overaction of the thalamocortical neurone and, as in the case of the true hallucinations, this should lead us to expect an irritative lesion of this neurone or a destructive lesion of the

sensorisensory neurone which would produce an overaction of the thalamocortical neurone by the process of hyperkinesis by defect.

SUMMARY

On the basis of laboratory psychology all mental functions can be reduced to the simple processes, sensation, association, reaction and inhibition. On the basis of this psychology the hallucinations are reduced to simple processes and the results are correlated with the anatomy of the nervous system. Psychology is carried into psychopathology for the purpose of making anatomic localizations.

The writer attempts to conclude from the patient's symptoms as to whether the pathologic process is an irritative one or a destructive one.

CONCLUSIONS

1. That it is possible to judge from the patient's symptoms as to the localization of hallucinations in any given case.

2. That the localization is usually in one of three foci, namely, the sensorimotor neurone, the sensorisensory neurone, or the thalamocortical neurone.

3. That the symptoms are evidence of hyperkinesis which takes place either by direct irritation of the neurone in question or by defect of any other neurone which seeks a final common path with the neurone in question.

4. That the symptoms of the patient are sufficient to tell the observer which process is at work, if he keeps the tenets of the psychology upon which the analysis is based, firmly in his mind.

REFERENCES

[1]Flechsig, Paul: Gehirn und Rückenmark—Wilhelm Engelmann, Lepsig, 1876.
[2]Campbell, A. W.: Histological Studies on Cerebral Localization—Proceedings of the Royal Society, 1903.
[3]Munsterberg, Hugo: Psychology, General and Applied, Appleton and Co., New York, 1914.
[4]Southard, E. E.: Literature Referring to "Hyperkinesis by Defect" and "Cortical Simplification."
[5]Sherrington, C. I.: The Integrative Action of the Nervous System, New York, 1911.
[6]Gosline, Harold I.: The Anatomical Implications of the Introspective Psychology, to be published.
[7]James, William: Textbook of Psychology.

The main body of the paper is a readaptation of Emil Kraepelin, Psychiatrie, 8te Auflage, Bd. I, Teil 2. "The Signs of Mental Disorder," a translation of the above is in preparation.

LABORATORY METHODS

THE ALKALIMETRY OF WHOLE BLOOD—A PRELIMINARY STUDY*

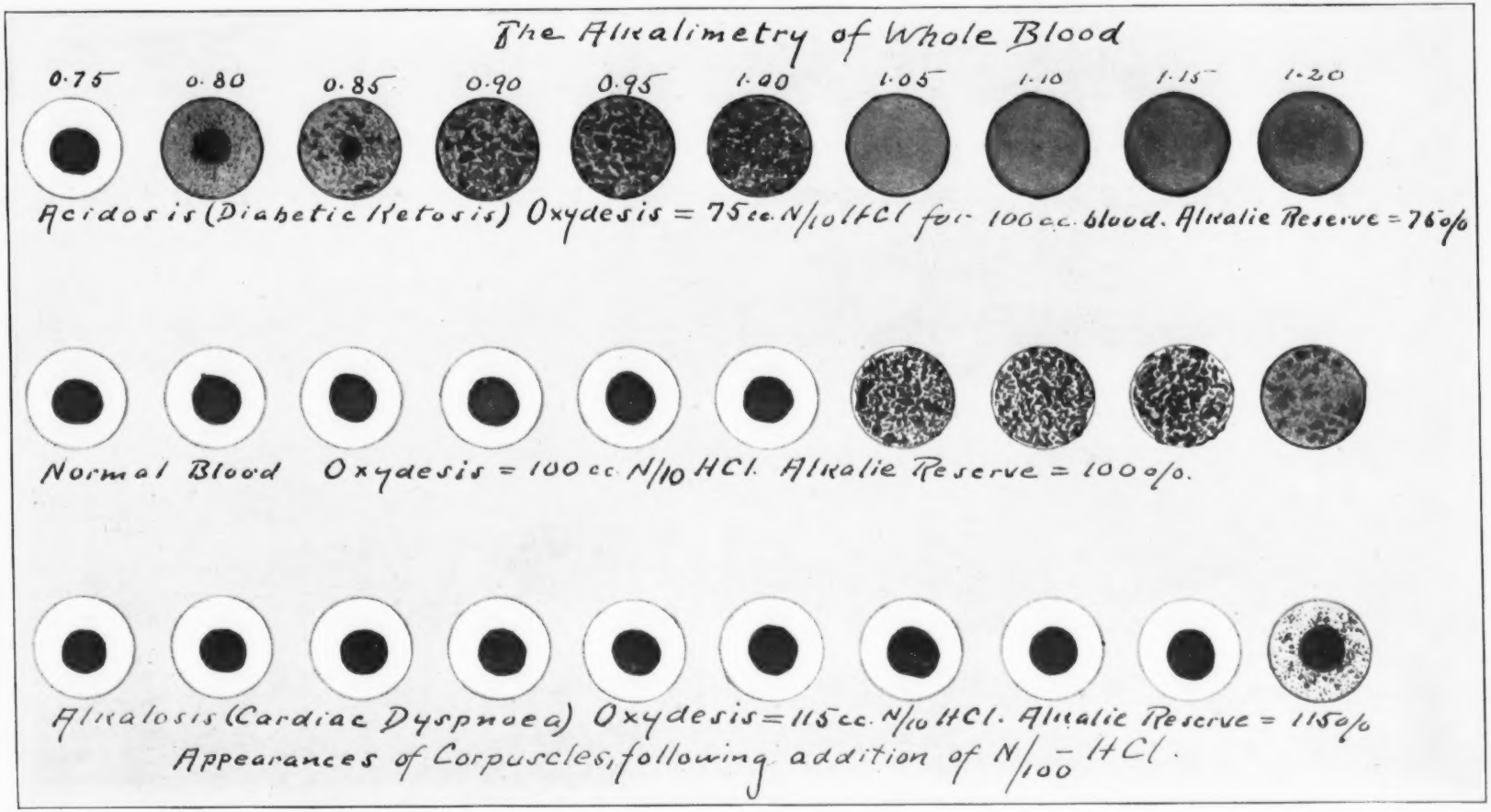
By John B. Rieger, S.M., M.D., Detroit, Mich.

IT SEEMS fair to assume that the alkali content of the circulating blood is in equilibrium with that of the tissues. A depletion of blood alkali therefore spells a corresponding depletion of alkali throughout the body. The methods devised on this basis for the estimation of the degree of acidosis have generally depended on the measurement of the bicarbonate content of the blood-plasma or the carbonic acid content of the alveolar air. Since increased pulmonary ventilation is really a compensatory process and demands for its maintenance an increased hydrogen-ion concentration of the blood, these methods will not detect the slighter grades of acidosis, such as may be caused by kidney lag. Such lag may be due to impairment of renal function, increased production of acid or both. When due to increased production of acid and the kidney function is normal, the index of acid excretion, devised by Fitz and Van Slyke[1] is the most delicate indicator of acidosis that we have. The test tells us nothing, however, about the amount of acid remaining unexcreted in the blood.

THE ACID-FIXING POWER OF THE BLOOD

For convenience, the acid-fixing power of the blood may be termed "oxydesis" (ὀξύ, acid; δέσις, to bind).† It is evident that the first effect of kidney lag is a back-up of acid salts (or basic salts) in the blood-stream, and the condition of acidosis or alkalosis may then be said to exist regardless of the acidity of the urine, the rate of ventilation, the carbonic acid content of the blood or of alveolar air. The hydrogen-ion concentration of the blood varies within such narrow limits in health that it may be said to be a constant. The oxydetic power of a unit volume of blood likewise represents an equilibrium between acid and base that in health approaches constancy. Indeed its relation to the hydrogen-ion concentration is much the same as the rim of the wheel to its hub. Henderson[2] believes that acidosis is even more common in pathologic states than fever. If oxydesis be a constant in health as the observations thus far made seem to indicate, any fall below the established figure will mean an impairment of renal function, an excessive production of acid or a depletion of the alkali-store of the body. Conversely if in certain pathologic conditions there occur an excessive production of alkali, and under the new conditions the kidney be able to selectively secrete basic phosphate, any increase beyond the normal oxydetic value of the blood will denote alkalosis, with perhaps kidney lag.

*From the clinic of Drs. Hugo A. Freund and Bruce C. Lockwood.
†Suggested by Dr. Max Ballin.


The Alkalimetry of Whole Blood
0·75
0·80
0·85
0·90
0·95
1·00
1·05
1·10
1·15
1·20
Acidosis (Diabetic Ketosis) Oxydesis = 75 cc. N/10 HCl for 100 cc. blood. Alkalie Reserve = 75%
Normal Blood Oxydesis = 100 cc. N/10 HCl. Alkalie Reserve = 100%.
Alkalosis (Cardiac Dyspnoea) Oxydesis = 115 cc. N/10 HCl. Alkalie Reserve = 115%
Appearances of Corpuscles, following addition of N/100 HCl.

A SIMPLE METHOD OF BLOOD ALKALIMETRY

Ten test tubes are set up in a rack. To the first is added 9 c.c. of an 0.85 per cent salt solution (chemically pure salt in distilled water) and 1 c.c. whole, fresh oxalated blood (avoid citrate). A Folin blood pipette or a 1 c.c. differential bacteriologic pipette may be used for charging the successive tubes. The blood is mixed with the saline by drawing it up in the pipette a few times, and bubbles are avoided by always keeping the tip of the pipette below the surface of the fluid. One c.c. of the diluted blood is placed in the bottom of each tube, avoiding the sides, and then starting on the left N/100 hydrochloric acid is added with a 2 c.c. differential pipette, increasing the amount by 0.05 c.c. with each tube. The tip of the pipette should be poised at least two inches above the surface of the blood to insure rapid diffusion of the acid, which should be dropped directly into the blood and not touched off on the sides of the tubes. The tube once charged should be immediately shaken and the set should not again be disturbed until the cells have completely settled. They should be kept in a cool place where there are no fumes. If no acidosis be suspected the first tube may be started with 0.70 c.c. acid, the last thus receiving 1.15 c.c. About fifteen minutes are required to charge the tubes and from one to two hours for settling, depending on their diameters. The last tube which shows the erythrocytes sharply settled in the center without any evidence of hemolysis in the supernatant fluid, gives the oxydetic value of the blood. The next tube to the right will generally show the corpuscles scattered over the bottom in an irregular manner giving a speckled appearance and in the tubes following, slight hemolysis will be noted. Sometimes hemolysis occurs without evident agglutination or swelling of the corpuscles. This will vary with their fragility. The oxydetic value of whole blood is then the greatest amount of acid that can be added to a unit volume without damage to its corpuscles. The bloods of fifty random subjects who considered themselves in good health and who gave no evidence of impaired kidney function, showed with the exception of two, an oxydesis of one hundred, i.e., 0.1 c.c. of blood can absorb 1.0 c.c. of N/100 hydrochloric acid, and 100 c.c. of blood absorbs 100 c.c. of N/10 acid, under the conditions described.

SOURCES OF ERROR

Sodium oxalate, in spite of careful purification, and in a concentration of 10 mg. to five c.c. of blood, has an appreciable buffer action, because of the weakness of oxalic acid compared with sodium hydroxide as a base. The erythrocytes of fresh blood, containing no oxalate are invariably damaged by 1.0 c.c. N/100 acid, but not by 0.95 c.c., while oxalated blood first shows an excess of acid in the 1.05 c.c. tube.

For the collection of blood, one ounce salt mouth bottles are utilized, and to each is added 1.0 c.c. of a 1 per cent solution of sodium oxalate, that has been several times recrystallized from distilled water. The bottles are gently warmed in an oven, to evaporate the water, and the oxalate is thus spread over a large surface, clumping is obviated, and the corpuscles are not damaged.

The syringe and needle used should have been boiled in distilled water and dried before use, to avoid dilution of the blood. The blood should not be used if it has stood more than an hour at room temperature. Placed immediately in an ice-box it is available for twenty-four hours.

Any kind of test tubes may be used, but they must be thoroughly cleansed in chromic acid and finally in distilled water, dried and stoppered as in bacteriologic work. The pipettes must be accurately calibrated and deliver clean. Test tubes of from ⅜ to 1 inch diameter and 6 to 8 inches in length have been preferred because the cells settle more rapidly the shallower the layer of blood.

When carefully performed, this method of alkalimetry is one of precision, and any inaccuracy in measurement or contamination of glassware is made evident by the presence of "sports" in the series, showing hemolysis or agglutination out of order. It is not of course academically correct to say that a unit volume of blood will fix a certain amount of acid, as determined by damage to the erythrocytes. It requires about 0.05 c.c. of N/100 acid to agglutinate the washed corpuscles and the oxalate somehow accounts for 0.05 c.c. more. However, the method gives promise of service in the diagnosis of early stages of acidosis, the prognosis of the more severe grades and the early recognition of impairment of renal function. Dr. Freund and the present author will report elsewhere the results obtained with alkalimetry on the blood of patients representing a variety of pathologic conditions as determined by other laboratory tests.

REFERENCES

[1]Fitz and Van Slyke: Jour. Biol. Chem., 1917, xxx, 389.
[2]Henderson, L. J.: Oxford Medicine, 1, Part 4, p. 389.

VARIATIONS IN THE WASSERMANN REACTION*

By Eric R. Wilson, A.B., Los Angeles, Cal.

WE FEEL that the acceptance of a positive Wassermann of blood serum showing either a weakly-positive up to a two-plus reaction as a final diagnosis in cases giving a negative history and symptoms and deeming this sufficient indication for immediate antiluetic treatment, without first considering the possible variations which are bound to occur under any and all circumstances, is doing a gross injustice to the average patient.

In a great many cases which we have observed giving negative symptoms and history, a positive blood serum reaction has been obtained varying from a decided negative with one antigen to a pronounced two-plus reaction with another kind of antigen.

As to the different kinds of antigens employed. We have found the ordinary alcoholic extracts of normal organs to be inferior in every respect to that of the acetone-insoluble extract of beef heart, and this in turn to be inferior to an alcoholic extract of normal organs reinforced with cholesterin. The writer invariably uses both the latter antigens in all Wassermann serologic tests.

The cholesterinized extract gives a quicker, sharper, and more sensitive reaction than the acetone insoluble antigen to such an extent as that of giving a faint but decided positive reaction with some normal blood sera.

Again it has been shown that a positive Wassermann is present in other diseases such as leprosy, hepatic disease and scleroderma, which are far remote from syphilis.

*From the Department of Pathology, Bacteriology, and Laboratory Diagnosis, College of Physicians and Surgeons, University of Southern California.

We have observed that from twenty-four to seventy-two hours after either chloroform or ether anesthesia a normal blood serum will sometimes yield a positive reaction.

A point of great interest is the variation of a reaction over short periods of time, especially is this true in the variation from a weakly-positive or suspicious reaction to one decidedly negative over a period of from seven to sixteen days.

We cannot help but believe that some of the variations are accounted for to a greater or lesser degree by metabolic irregularities, especially when the physiologic balance of lipoid metabolism becomes disturbed.

We cannot too strongly emphasize that the tubes used for collecting the samples of blood to be tested be sterilized and that all sera should be tested as soon after collection as possible. We have repeatedly demonstrated that anti-complimentary substances develop in the sera if it be kept for considerable time, which not only inhibit hemolysis in the antigen and control tubes but certain substances are formed presumably by bacterial growth or bacterial action on some substance in the blood serum creating an inhibition of hemolysis in the antigen tubes alone, causing perhaps a negative serum to become positive.

In conclusion we earnestly plead that all facts be considered which may cause these variations before accepting as final a positive Wassermann test in which both history and symptoms are known to be negative.

BIBLIOGRAPHY

Kolmer: Infection, Immunity and Specific Therapy, 1917, W. B. Saunders Co., pp. 443-447.
Craig: The Wassermann Test, 1918.

SOME REMARKS ON THE QUESTION OF THE LEUCOCYTES IN ANAPHYLAXIS OF SERUM SICKNESS

By Jacob Rosenbloom, M.D., Ph.D., Pittsburgh, Pa.

In a recent article Barach[1] has reported a study of the changes in the leucocytes in a case of serum sickness with a delayed anaphylactic reaction.

In this case he reports that *no* eosinophilia was present and on this account he states that eosinophilia is not a criterion of anaphylactic reaction.

I would like to call attention to the fact that *acute* anaphylactic shock and the ordinary serum sickness are characterized by a leucopenia with a reduction of the polynuclear cells and *no* change in the eosinophiles.[2] We expect eosinophilia in this relation only in cases of *nonacute* sensitization and as the case reported by Barach is an acute one, eosinophilia would naturally not be present.

REFERENCES

[1]Barach: Leucocytes in Anaphylaxis of Serum Sickness, Jour. Lab. and Clin. Med., 1920, v, 295.
[2]Bienenfeld: Das Verhalten der Leukozyten bei der Serumkrankheit. Jahr. f. Kinderheilk., 1907, lxv, 174.
Herrick: The Eosinophilia of Bronchial Asthma with Report of a Case Showing Extreme Blood Changes, Jour. Am. Med. Assn., 1911, lvii, 1836.

A MACHINE FOR SHAKING BLOOD COUNTING PIPETTES*

By Russell L. Haden, M.D., Detroit, Mich.

IN LABORATORIES where many routine red and white blood counts are done each day much time is consumed in shaking the pipettes by hand. A pipette shaking machine in use at the Mayo Clinic has been described by Little. This machine carries only two pipettes at a time and is rather complicated.

For the past two years we have used in our laboratory a pipette shaking machine designed and made for us by Eberbach & Son Company, of Ann Arbor, Michigan. We have found that much time is saved by its use and that more satisfactory preparations are obtained in the counting chamber, due to the more uniform suspension of cells in pipettes shaken mechanically.

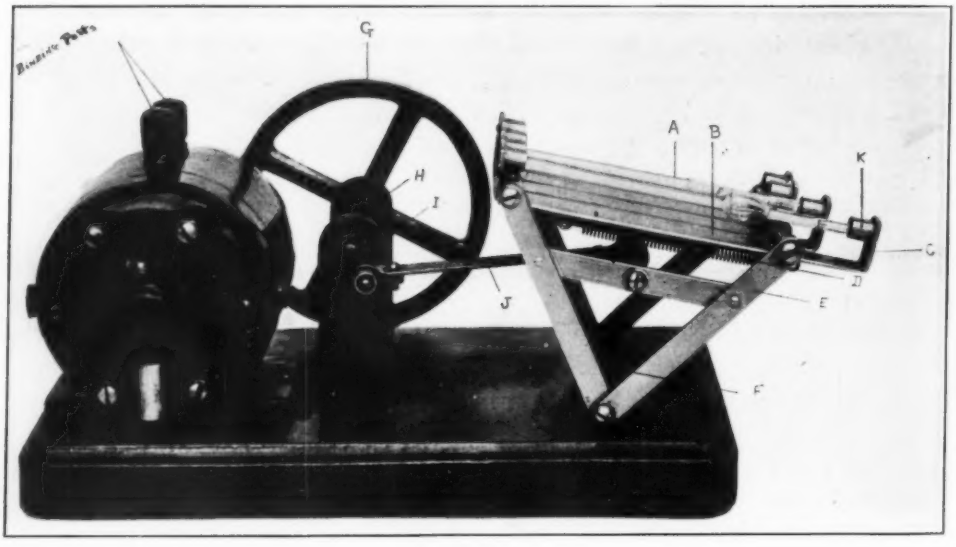


Fig. 1.

Fig. 1 shows all the essential details of the instrument. The base is a heavy cast iron block measuring 10 x 5½ x 1 in., set on rubber supports to diminish vibration. A one-sixteenth horse power motor is fastened to one end. On the other end is a pipette holder block (*A*). Each holder (*B*) is separate and can be adjusted to any length pipette by means of an arm (*C*) sliding in a groove and held in place by a spring (*D*).

The pipette holder block is attached to the base by a metal V-shaped frame (*E*) with shaft at (*F*).

Between the motor and pipette holder block there is a 4 in. wheel (*G*) connected by a belt to the spindle of the motor. To the counter shaft (*H*) of the

*From the Laboratory Department, Henry Ford Hospital, Detroit, Mich.

wheel is attached a crank (*I*) which is connected with the under part of the pipette holder block by a straight metal piece (*J*).

The pipettes are held in place by small cups (*K*) on the holders. Each cup is half filled with a solid soft rubber plug which prevents leakage of fluids and breakage of pipettes. It is necessary to have a rheostat to control the speed of the motor. This is placed under the laboratory table. The switch is in a similar position.

With the machine in motion the pipettes have a to and fro motion through an arc similar to that described in shaking pipettes by hand.

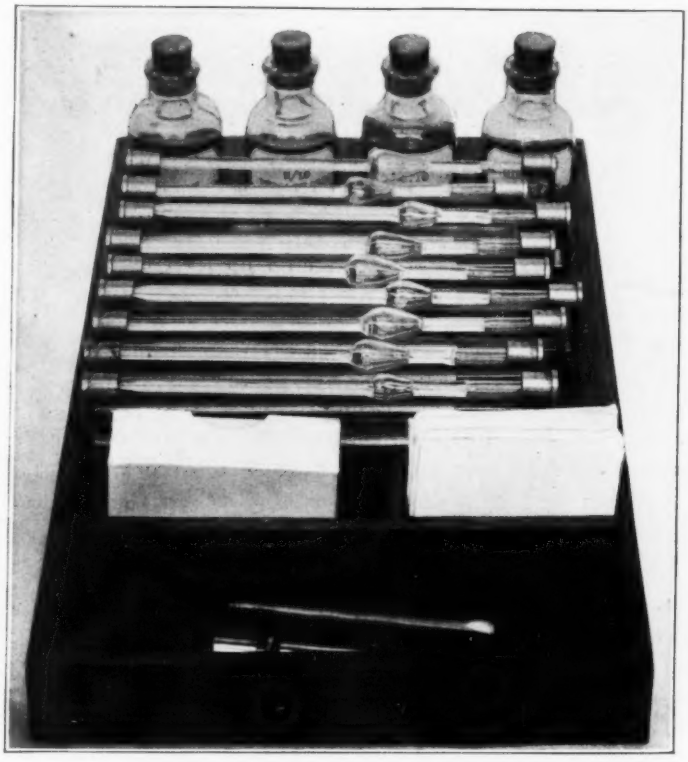


Fig. 2.

The block can be made to hold six or eight pipettes if desired. The machine can be easily adapted for other shaking purposes.

A spring clamp fitting over the cups of the outer holders enables one to use an Erlenmeyer flask. A small test tube can be used by putting a match stick through the cork and fitting it into the cup.

Similarly a frame to contain small bottles held in place by the pipette holder has been used.

The very convenient pipette holders have been made use of to hold pipettes on a tray used in collecting blood for counts in the hospital wards.

The tray Fig. 2 is shown in the accompanying photograph. It measures 6 x 10 x 1 in. The holder is similar to those on the shaking machine. The spring securing the sliding arm in the groove is placed on the upper instead of under

side of the holder. Four holes are bored in one end of the tray to hold 20 c.c. bottles containing N/10 hydrochloric acid, Hayem's solution, dilute acetic acid, and alcohol. Compartments at the other end are provided for cover slips used in making blood films, and for pipette rubbers, blood lancet, and camel's hair brush.

The tray assembles in a convenient way everything needed to do blood counts. The holders prevent leakage of the fluids from the pipettes after filling, and diminish breakage.

A SATISFACTORY METHOD OF DEMONSTRATING GASTRIC MOVEMENTS ON A SMALL ANIMAL. COMPARATIVE STUDIES II*

By T. L. Patterson, M.A., M.Sc., Iowa City, Ia.

RESULTS of recent studies on the movements of the empty and filled stomach in some of the lower animals would make it seem desirable to record briefly a method of demonstrating gastric activity, inasmuch as it is quite satisfactory even in the hands of an amateur.

The methods of registering gastric movements in both hunger and digestion which have been conducted largely on man and the higher laboratory animals make it inconvenient for many of the smaller institutions to adopt due to a lack of proper facilities and equipment. Furthermore, in the case of the larger laboratory animals it requires several days of training before the animals are even in a condition for giving normal physiologic reactions, which is more time than can ordinarily be allotted to a single laboratory experiment. In addition, any disturbing influence, such as noise, tends to affect the animal, leading immediately to a more or less prolonged inhibition of the gastric movements, so that again, these animals in which quietness plays such an essential role are not best adapted for general laboratory use, and especially where the classes are of considerable size.

The method I have devised is based on three general principles: 1. On the balloon method of registration. 2. On an easily obtainable animal, the bullfrog (Rana catesbiana), the common species of frogs not being suitable on account of their smallness. 3. On the operation of stomostomy.

This very simple operation, requiring but a few moments for its completion after the anesthetization of the animal and without aseptic precautions, consists of making a circular opening on one side between the ramus of the inferior maxillary near the posterior angulosplenial region and the anterior cornua of the hyoid bone through the skin, the submaxillaris (mylohyoideus) muscle and the lining membrane of the pharyngo-oral cavity of about 8 mm. in diameter (Fig. 1). This operation may be bloodlessly performed, provided care is taken to avoid injury to the superficial mandibular vein (Vena maxillaris inferior)

*From the Physiological Laboratory, Queen's University, Kingston, Canada.

which courses along the insertion of the submaxillaris muscle and turns inwards at its hinder border to join the lingual vein.[1]

The gastric balloon is constructed from the lower portion of a condom which is of very delicate rubber, so that it will record definitely the stomach's activity. This is securely tied to one end of a long, flexible rubber tube (outside diameter 4 mm.), which contains a short piece of glass tubing (6-8 mm. in length) and of such a size as to slip easily into the lumen at the end of the tube thus preventing its occlusion. The balloon after being connected to the tube as above should be about 6 cm. in length (Fig. 2).

The stomostomy usually heals in from three to four days so that the animal is ready for physiologic study and the fast should be commenced a day or so previous to the operation. Through this opening the balloon may be introduced

Fig. 1.—Ventral view of frog's head showing location of stomostomy at S.

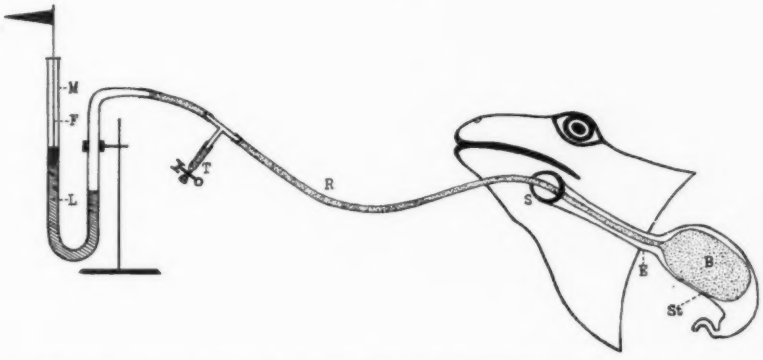


Fig. 2.—Diagram showing method of recording gastric movements of the frog's stomach. *B*, rubber balloon in stomach. *M*, manometer. *F*, cork float with recording flag. *L*, manometer liquid (water). *R*, rubber tube connecting balloon with manometer. *T*, side tube for inflation of stomach balloon. *S*, stomostomy. *E*, esophagus. *St*, stomach.

by means of a glass seeker and then by opening the frog's mouth it may be carefully pushed into the stomach with the seeker through the short esophagus, which may be greatly enlarged, yet when empty is completely closed by folding of the walls. To accomplish this, set the frog against the side of a sink or box, grasp it with the left hand around the shoulders and body, then with the forefinger of the same hand raise the head slightly and proceed as above. The balloon should be inflated two or three times after its introduction into the stomach in order to straighten out the folds before being connected with the manometer. In this manner the small rubber tube lies under the free edge or at the side of the tongue, passes through the stomostomy to the side tube and thence to the manometer carrying the float. In this position the balloon may be inflated through the side tube until the manometer indicates a pressure of about 2 cm. which has proved to be the best pressure for recording stomach movements of this

animal. By this method, the stomach pressure fluctuations are transmitted by air transmission to the surface of the liquid in the manometer and recorded graphically by the writing point of the float on a 50 to 60 minute drum, without any danger of it being interrupted by the animal biting on the rubber tube, as would be the case if the tube passed between the jaws. The animal during the experiments or when tracings of the gastric movements are being recorded may be placed in a small laboratory sink about 7 x 10 x 5 inches, or if this is not available any other small compartment may be used. In either case, the bottom should be covered with filter paper, kept well moistened and the top covered with the exception of a very small opening to admit air and the rubber tube or tubes of the apparatus.

With this arrangement the animal is well concealed from most disturbing influences and the sinks or other compartments being darkened by opaque covers,

Fig. 3.—Normal contractions of the empty stomach of the frog after a fast of four days.

the animal feels itself securely hidden and will remain quiet for long periods of time unless directly disturbed which always leads to a more or less prolonged inhibition of the gastric movements.[2-3] The introduction of the balloon itself will lead to a temporary inhibition lasting usually from 20 to 50 minutes and if the animal is being used for the first time typical and regular contractions of the stomach may not be obtained for a much longer period. The best way to deal with a new animal is to introduce the balloon and then leave it entirely alone, unless it throws out the balloon in which case replace it as often as it occurs.

The gastric hunger contractions of the frog are practically continuous, with no indication of any periodicity, while the tonus changes of the stomach musculature are so slight as to be practically a negligible factor and for this reason only one type of hunger contraction is exhibited. This particular type of contraction shows an average duration of about one and three-fifths minutes, and the intervals between the contractions vary from sixteen to thirty-three seconds. These contractions are remarkably strong, sustaining a column 15 to 22 cm. high.

The contraction phase is abrupt, while the relaxation is slower. The curve is perfectly smooth, showing no smaller superimposed waves and no indication of the contractions falling into groups separated by periods of relative quiescence, as is the case in all the higher animals (Fig. 3). The amplitude of these contractions increases during prolonged fasting, but there is no obvious increase in tonus.

For the digestive movements, the cannibalistic bullfrog may be fed a couple

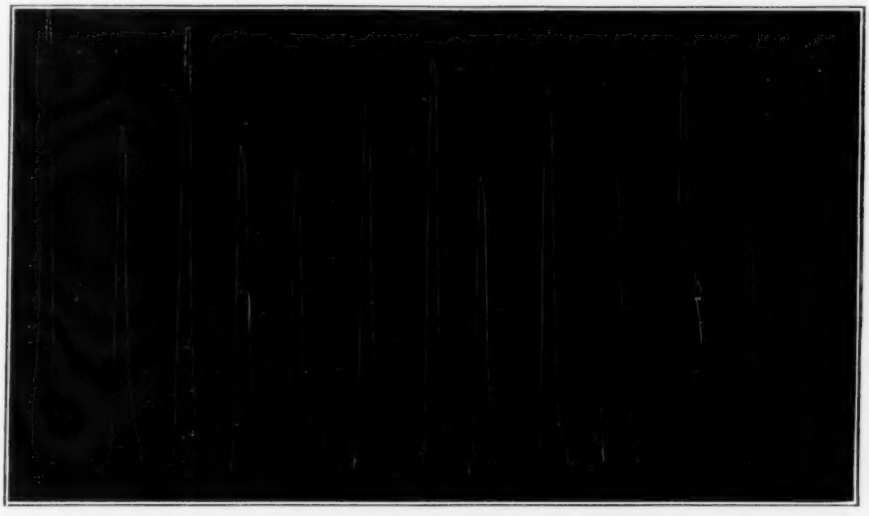


Fig. 4.—Normal digestive peristalsis of the frog's stomach four hours after feeding two live grass frogs.

Fig. 5.—Normal contractions of the empty stomach of the frog after a fast of five days, showing inhibition from introducing directly into the stomach at X, 5 c.c. of 0.5 per cent solution of hydrochloric acid.

of live grass frogs and the balloon reintroduced into the stomach after thirty to sixty minutes to allow sufficient time for the asphyxiation of the ingested frogs. The digestive peristalsis when compared with the normal hunger records shows but very little change from the stomach of the animal in hunger, the only observable variation being a slight increase in the rate of the contractions (Fig.

4). Figs. 3 and 4 probably show the maximal variation of increased rate, for more often there is much less differentiation between these two conditions.

The inhibition of the gastric hunger contractions may be studied on the frog by introducing slowly through a second rubber tube, one end of which is attached to the balloon end of the first tube, such substances as water, sodium carbonate, 1 per cent solution, and hydrochloric acid, 0.5 per cent solution, in amounts of about 5 c.c. These substances invariably produce temporary inhibition, the duration depending on the nature of the substances introduced, it being the most marked in the case of the acid and least with the water (Fig. 5). These inhibitory effects may also be produced on the digestive movements of the frog in the same manner, but such substances do not inhibit the digestive peristalsis in the higher animals.

REFERENCES

[1]Ecker, A.: The Anatomy of the Frog (transl. by George Haslam), Oxford, 1889, pp. 34, 62, 64, 242.
[2]Patterson, T. L.: Am. Jour. Physiol., 1916, xl, 140.
[3]Patterson, T. L.: Am. Jour. Physiol., 1916, xlii, 56.

The Journal of Laboratory and Clinical Medicine

VOL. V. JULY, 1920 No. 10

Editor-in-Chief: VICTOR C. VAUGHAN, M.D.
Ann Arbor, Mich.

ASSOCIATE EDITORS

DENNIS E. JACKSON, M.D. - - CINCINNATI
HANS ZINSSER, M.D. - - - NEW YORK
PAUL G. WOOLLEY, M.D. - - DETROIT
FREDERICK P. GAY, M.D. - - BERKELEY, CAL.
J. J. R. MACLEOD, M.B. - - - TORONTO
ROY G. PEARCE, M.D. - - AKRON, OHIO
W. C. MACCARTY, M.D. - ROCHESTER, MINN.
GERALD B. WEBB, M.D. - COLORADO SPRINGS
WARREN T. VAUGHAN, M.D. - . BOSTON

Contents of this Journal Copyright, 1920, by The C. V. Mosby Company—All Rights Reserved
Entered at the Post Office at St. Louis, Mo., as Second-Class Matter

EDITORIALS

Pneumoperitoneum and Abdominal Diagnosis

INFLATION of the peritoneal cavity for diagnostic purposes is a relatively recent innovation. The first instance on record, however, in which this method was employed on human beings occurred eighteen years ago, when Kelling introduced oxygen into the abdominal cavity in a case of ascites and in one of gastric carcinoma.

Oxygen inflation of body cavities as an adjuvant in the use of the roentgen ray has long been in use. The lungs, naturally air-containing, indicated to the early observers the advantages, and air injection into the bladder, the renal pelves, and joint capsules has become quite a common procedure. Conversely, the x-ray has frequently been employed to control lung collapse in artificial pneumothorax. Air inflation of the stomach has been used in roentgenology for study of that organ as well as surrounding organs, particularly for the diagnosis of pericardial effusion. The air-containing colon throws the spleen into good relief on the x-ray plate. Ventriculography, the raying of air-filled cerebral ventricles, has been decidedly helpful in cases of internal hydrocephalus and in the diagnosis and localization of certain brain tumors.

The pioneer workers in pneumoperitoneum introduced air or oxygen into

the abdominal cavity in cases of ascites after withdrawing the fluid, employing therewith the method of endoscopy or laparoscopy. Using the Jacobus endoscope in the same manner as the urethroscope and cystoscope are used, they were able to study the appearance of the abdominal organs, particularly the liver, over a limited area and without operation. This method never proved extremely successful and could be used in such a small number of cases that it has never come into general practice.

Later it was found that gas could without harm to the patient be introduced into the peritoneal cavity of nonascitic individuals. Roentgenograms of individuals so treated have shown that the parenchymatous organs of the abdomen and pelvis, particularly the liver, spleen and kidneys, may be brought into as clear detail as are the heart and lungs in thoracic plates. The following types of diseases have been diagnosed by this method: carcinoma of the liver; hepatic cirrhosis; other tumors and irregularities of the liver and spleen; peritoneal carcinosis and cancer nodules on the diaphragm; gall stones and other lesions in the region of the gall bladder; peritoneal adhesions, particularly to the anterior abdominal wall; carcinoma of the ascending colon; cystic ovaries and uterine myomata; enlarged mesenteric glands; echinococcus cysts of the liver.

Detail of the kidneys, while not as clear as that of the liver and spleen, is decidedly better than that of the ordinary renal plate.

The technic of gas inflation has been variously described by different authors. The patient must be prepared as for bismuth studies, the intestines being thoroughly cleansed and the bladder emptied. The patient lies on his back. The skin of the abdomen is scrubbed and painted with iodine over the area selected for paracentesis. This point is usually a little to the left of and below the umbilicus. If adhesions are supposed to be present in a certain area or if there is a scar of an old operation it is important to avoid such area. The skin is anesthetized with an ethyl chloride spray, an ordinary lumbar puncture needle is passed in obliquely, and cautiously pushed through the fascia into the peritoneum. The stylet is removed, the needle connected by a sterile rubber tubing to an oxygen tank, and sufficient oxygen is allowed to flow into the cavity until the abdomen becomes dome-shaped or the patient complains of distention or mild painful sensations between the shoulders. The gas is then cut off and the needle withdrawn. From two to four liters of oxygen are usually required. The injection should take from ten to twenty minutes' time.

The volume of gas may be controlled and measured in a system of bottles similar to those used in producing artificial pneumothorax. The air or oxygen may be bubbled through sterile warm water. Some German writers, notably Schmidt and Rautenberg use an ordinary air bellows to produce inflation. The tendency appears to be towards simpler methods, but these should not be adopted at the price of increased risk of infection. With an oxygen tank the volume administered may be measured by attaching a rubber bag similar to that used in gas-oxygen outfits. As a rule the oxygen or air is not sterilized. During abdominal operations the peritoneum is exposed to nonsterile atmospheric air and this of itself does not result in infection. No untoward results in infection have so far been reported following pneumoperitoneum.

There seems to be little or no danger of injuring a loop of intestines. If a

needle be passed through the abdominal wall of a rabbit the intestines are found to always recede before the sharp point. After death the intestines are easily punctured in this way. Pneumoperitoneum practiced on well over two hundred cases has resulted in no reports of injury to the intestines. Care in introducing the needle slowly and the usual surgical asepsis should of course always be rigidly observed.

Schittenhelm suggests a method of puncture which should appeal as enabling the operator to know definitely when the point of the needle has entered the peritoneal cavity. He has attached to the lumbar puncture needle an all-glass syringe containing physiologic salt solution. During the slow passing of the needle through the abdominal wall, gentle pressure is exerted on the plunger of the syringe. When the liquid flows easily the cavity has been reached.

Fluoroscopic examination is quite satisfactory. Plates are especially valuable. For best results it is important to take plates through several planes and with the patient in different positions. The principle to be borne in mind throughout is that the organ to be studied should be in the highest possible plane so that it will be surrounded by air and the intestines will fall away and not obstruct the view. For studies of the liver and spleen the patient should be upon his abdomen and the head end of the table should preferably be slightly raised. For plates of the right or left kidney he should lie on his left or his right side as the case may be, the tube should be in front of his abdomen and the plate at his back. For pelvic studies he should lie on his abdomen and the foot end of the table should be raised about 15 degrees. The intestines will then fall out of the pelvis. The tube is placed beneath the table and focussed on the promontory of the sacrum. Studies of the anterior abdominal wall for adhesions or other pathology of the peritoneum, are made with the patient supine, the rays being directed transversely through from side to side.

For examination of the stomach Schmidt recommends air inflation of that organ just preceding inflation of the peritoneal sac. Transverse plates with the patient supine after such preparation show excellent pictures of such conditions as carcinoma of the lesser curvature. Colonic inflation in the same way will often show pathology in that portion of the intestines or will improve the picture of the spleen or left kidney.

The procedure is not without some inconvenience to the patient. With a gas-filled abdomen he frequently suffers an unpleasant feeling of distention or he may complain chiefly of dyspnea. If he stands up he may have rather severe pain in the region of the shoulders, particularly the right. The gas is usually resorbed within 24 to 48 hours, but the patient, if he does not remain in bed, may be quite uncomfortable for three or four days. Two remedies for this drawback have been suggested. Schmidt uses a special needle of the same size and shape as a lumbar puncture needle and bevelled at the tip, but with a solid tip and a stopcock at the proximal end of the needle. The air enters the peritoneal cavity through a side slit just behind the solid tip. After the abdomen has been filled, he leaves the needle in place with stop cock closed. When the examination is completed he opens the cock and allows the air to slowly escape. Gentle pressure in the flanks aids in the deflation.

Alvarez uses instead of air or oxygen, carbon-dioxide gas. This is ab-

sorbed very rapidly and produces no apparent ill effects. It is usually all absorbed within a half hour—so rapidly in fact that considerable skill is required to take all necessary plates before too much of the gas has disappeared.

Pneumoperitoneum represents a diagnostic method of value equal to that of bismuth studies. The two methods are not competitors. Whereas, the latter is useful in the study of pathology of the stomach and intestines, the former enables us to gain further information of the parenchymatous organs of the abdomen. With the exception of some discussion of the temporary discomfort of the patient, all reports so far have been very favorable to the procedure. It is certainly a valuable diagnostic method, but the enthusiasm of the pioneer workers must not allow us too great a sense of security. A new method that fills so great a need as does this will probably be used very widely and at times perhaps a little carelessly. A few unnecessary accidents have been known to bring good methods into disrepute. Thorough physical examination should always precede the operation, particular attention being devoted to study of the cardiovascular apparatus. Carbon dioxide would not be used where there is any possibility of a tendency to acidosis. Until the technic has been mastered cases should be treated as hospital patients and watched during return to normal.

REFERENCES

Stein, Arthur, and Stewart, William H: Roentgen Examination of the Abdominal Organs Following Oxygen Inflation of the Peritoneal Cavity, Ann. of Surg., 1919, lxx, 95.
Stewart, W. H., and Stein, A.: (Same Title), Am. Jour. Roent., 1919, vi, 533.
Schittenhelm, A.: Reviewed in Am. Jour. Roent., 1919, vi, 584.
Rautenberg, E.: Pneumoperitoneale Röntgendiagnostik, Deutsch. med. Wchnschr., 1919, No. 8, p. 203.
Schmidt, Adolf: Ein Neues Verfahren zur Röntgenuntersuchung der Bauchorgane, Deutsch. med. Wchnschr., 1919, No. 8, p. 201.
Alvarez, Walter C.: California State Jour. of Med., February, 1920.
Whitman, Armitage.: Oxygen Inflation of the Peritoneal Cavity: a Personal Experience, Jour. Am. Med. Assn., 1920, lxxiv, 1021.

—*W. T. V.*

Recent Work On Vitamines

EVEN when the requirements of the animal body for calories and protein building stones are fully met, the diet will fail to maintain health unless it also contains substances of unknown chemical nature called "accessory food factors" or "vitamines." These are entirely of plant origin, and require to be taken only in very small quantities to display their beneficial action. They do not become rapidly destroyed in metabolism, but may remain attached to the tissues for a sufficient time so that carnivorous animals obtain them indirectly.

Serious and prolonged absence of certain vitamines from the dietary may hinder the growth of young animals or may be the cause of serious disease in adults. Great advancement in our knowledge of vitamines had been made in recent years, particularly through the work of F. Gowland Hopkins and Hariette Chick,[1] Osborne and Mendel,[2] Funk[3] and McCollum.[4]

There are at least three different vitamines which are characterized partly

by the nature of the diseased condition which their absence from the diet occasions, and their influence on the growing animal, and partly by their solubilities.

The human diseases which are known definitely to be due to the absence of one or other of the vitamines are beriberi, scurvy, and rickets, and accordingly three vitamines are distinguished:

1. Antiberiberi or antineuritic vitamine (also called water-soluble "B" growth factor).
2. Antirachitic vitamine (also called fat-soluble "A" growth factor).
3. Antiscorbutic vitamine.

Investigation of the distribution of these factors among the various foodstuffs, and their degree of stability towards heating, etc., has been very materially facilitated by the fact that certain of the lower animals suffer diseases like those seen in man when vitamines are absent from the diet. This renders it possible to prosecute the investigations intensively and under scientifically controlled conditions, thus affording us the knowledge which enables us to alleviate human suffering.

The Antiberiberi or Antineuritic Vitamine.—Beriberi is a disease characterized either by wasting, anesthesia and paralysis, or by excessive edema. Pathologically, it is a form of severe neuritis. It is common in rice-eating communities, and the first clue to its precise cause was afforded by the observations that it does not occur among people who take unmilled rice, and that it disappears in those who take "polished" rice when the millings, or a watery extract of them, (pericarp and germ) are added to the diet. It was observed by Eijkman that the poultry of a prison where beriberi cases occurred exhibited symptoms very like those of the human disease, and further investigation showed extensive nerve degeneration to exist in the affected animals. Pigeons fed on polished rice develop exactly the same symptoms so that experimental investigation soon rendered it possible to determine with accuracy which foodstuffs prevent beriberi, and the further properties of the active substance.

Meanwhile McCollum and Davis[4] discovered that the absence of the same water-soluble vitamine interfered seriously with the growth of young animals. The withdrawal of the vitamine causes an immediate cessation of growth followed by a period during which the body weight remains more or less constant, but ultimately declines. During this stage muscular incoordination is a prominent symptom, and death ultimately occurs. This vitamine disappears from the organism immediately it is withdrawn from the food and the animal cannot synthesize it.

This vitamine is present in abundance in the seeds of plants and the eggs of animals. It is very plentiful in yeast and in yeast extracts, which may therefore be added to the diet when there is risk of its deficiency. It is absent from bread made with white wheat flour, but beriberi is rare in people living on this food, since other foodstuffs containing the vitamine are usually also taken. Beriberi is unknown where rye bread is a staple food.

The Antirachitic Vitamine (Fat-soluble "A" Factor).—The first inkling to the existence of this factor we owe to Stepp who found that mice could not live for long on foods from which all fatty substances had been thoroughly extracted by alcohol and ether. If the extract was restored to the extracted food, this again

became adequate. Hopkins then showed in carefully controlled work that animals (rats) not only failed to grow, but declined and died when they were fed on artificial diet composed of the purified constituents of milk, although they might eat voraciously. The addition of a few drops of milk, insufficient to raise the energy or protein-value appreciably, invariably caused normal growth to return. Osborne and Mendel also found that although rats grew for about two months upon a diet containing protein, protein-free milk, starch and lard, they ultimately declined, but that this decline could be avoided by substituting butter for the lard, and that the active substance was concentrated in the butter-fat portion of the butter. Later work by various investigators showed that most animal fats, but not those of plants, contain this essential, and it was hence called fat-soluble A factor vitamine. Lard does not contain it, so that young animals fed with this as the only fat of an otherwise perfect diet fail to grow. An important difference will be observed in the curve of growth of young animals in the diet of which the factor B is alone deficient, namely that a small amount of growth continues for a time after the removal of the proper diet. This indicates that there must be some reserve of the fat-soluble vitamine in the body, and that it is only after this is exhausted that growth entirely ceases and decline then sets in.

When the reserves of the fat-soluble vitamine are exhausted, not only do the young animals fail to grow, but they become highly susceptible to bacterial disease, one symptom of which is a very characteristic eye infection (xerophthalmia) which begins with a swelling of the lids, and later develops into a purulent conjunctivitis, often leading to blindness. Administration of some fat-soluble vitamine in the diet dispels the eye symptoms usually within a few days. When the dietary of adult animals contains none of this vitamine the eye symptoms also develop, the general condition greatly deteriorates and the animals become extremely susceptible to bacterial infections, particularly those affecting the lungs, and from which they readily succumb. Adults are, however, much less susceptible to the absence of the fat-soluble vitamine than growing animals. This may be because of great storage capacity for it.

At the same time it is worthy of note that there is reason to believe that the condition known as war edema is due to a deficiency of this vitamine. It may be stated here that when both the A and B factors are absent from the diet young animals immediately cease to grow and develop the nervous symptoms due to the absence of the B factor, from which they usually succumb before the symptoms due to the absence of the A factor have had time to develop.

A most important relationship probably exists between this vitamine and the occurrence of *rickets*. Thus, when the puppies of large dogs are fed with separated milk, bread, linseed oil, yeast and orange juice, they grow at a normal rate, but in about six weeks develop undoubted symptoms of rickets (bones defectively calcified so that the long bones bend, swelling at the epiphyses, a rosary at the costochondral junctions, the ligaments loose, general lethargy and loss of muscular tone). In this diet both the water-soluble and the antiscorbutic factors are present in abundance (the yeast and the orange juice), but the fat-soluble factor is very low. Evidently linseed oil contains a sufficient trace of this factor to allow of an abnormal form of growth in puppies. When animal fats, such as cod liver

oil or butter, are substituted for the linseed oil in the above, or a similar diet, rickets does not occur. It should be noted, however, that lean meat and meat extracts contain more of the antiscorbutic factor than can readily be attributed to the amount of fat in them.

There are two main sources for the fat-soluble vitamine, (1) certain animal fats, and (2) green leaves. It is particularly abundant in cream, butter, beef fat, fish oils (particularly cod liver oil and whale oil) and egg yolk. It is absent or present only in traces in most vegetable oils, such as linseed, olive, cotton seed, but in some of them such as peanut oil it is present in larger amounts.

Its presence in green leaves stands out in contrast to its absence from root vegetables. It is also present in certain cereals and pulses.

The Antiscorbutic Vitamine.—That this, at one time so prevalent, disease is definitely due to the absence in the dietary of some vitamine has been known in a general way for a long time. It used to be very common among the crews in the days of sailing ships, and nautical history records many interesting observations by captains and ship's surgeons showing that it could be prevented by adding certain fruits or the juices of fruits or vegetables to the daily ration. Indeed lime juice became a regular part of the mariner's ration. Great progress was made in the investigation of the precise distribution and behavior of the antiscorbutic vitamine by the discovery that guinea pigs develop the disease when all green stuff was removed from the diet and the animals were fed on grains and water or autoclaved milk. The symptoms appear in about 20 days, up to which time if young animals are used the growth curve continues. The symptoms of *postmortem* findings, similar to those seen in man, (tenderness and swelling in the joints, swelling of the gums, loosening of the teeth, tendency to hemorrhages and fractures of the bones). The curve of growth declines, and the animal dies usually about the 30th to 40th day. Important work is being done in the Lister Institute in London to determine the minimal amounts of various foodstuffs that are required in the scurvy diet to prevent the occurrence of the disease.

Regarding distribution it may be said that this vitamine is found in nature in all tissues which are actively undergoing metabolic change. It is abundant in growing green leaves, in fruits and in germinating seeds. But it is absent, or present only in traces, in dormant seeds, or in plant tissues that have been dried. It is also present, though less abundant, in fresh animal tissues and in milk. Although potatoes do not contain much of this vitamine, a diet composed mainly of them is seldom scorbutic because of the large quantities that are usually consumed. Canned vegetables and meats only contain traces of it because it is destroyed by the heating process. Canned fruits, however, contain more of it because it is preserved by the acid.

REFERENCES

[1]Hopkins, F. Gowland, and Chick, Hariette: Med. Research Committee National Health Insurance, Special Report No. 38, 1920, H. M. Stationary Office, Imperial House, Kingsway, London, W. C. 2.
[2]Osborne, T. B., and Mendel, J.: Jour. Biol. Chem., 1917, xxxi, 144.
[3]Funk, C.: Ergebnisse der Physiologie, 1913, xiii.
[4]McCollum, E. V.: Harvey Lectures, 1919, J. B. Lippincott Co., New York.

—*V. C. V.*

The Financial Support of Medical Education

IT IS highly gratifying to note the liberal way in which medical education in this country is being supported. These financial provisions are coming from the state and from private endowment, and both are welcome and at the same time are evidences of the high appreciation placed on the medical profession both by governmental agencies and by private individuals.

Under the influence of Thomas Jefferson the State of Virginia was, if we remember correctly, the first in the Union to make provision for the education of medical students. When the territory of the Northwest was partitioned and divided into territories, which subsequently became states, provision for state medical education was made by Indiana and Michigan. For many years the University of Michigan Medical School was the most important and prominent of all state university medical schools. This institution was opened in 1850 and has now passed through seventy years of its existence. The Legislature of 1919 made, without a dissenting vote, liberal appropriation for the medical school. This indicates that after seventy years of trial the state is satisfied, or at least well pleased, with the work which has been done by its medical school. During these seventy years state medicine has developed gradually, but constantly and healthfully, in Michigan. From time to time the Legislature of the State has passed acts which have provided for the treatment of certain people in the state, either at state or county expense. There is not in the state a cross road from which some individual has not come to University Hospital, received treatment and been benefited thereby. University Hospital is, therefore, regarded by the legislature as one of the most efficient institutions in the state. From every county patients are sent to this hospital each year. Poor people of respectability are kept from passing into the bounds of pauperism by being relieved of their physical disabilities. One act of the legislature provided for the treatment of children whose parents or guardians are unable to pay. This worked so well and the beneficial results were so in evidence that a few years later an act was passed to provide free hospital service and medical and surgical treatment for persons afflicted with a malady or deformity which can be benefited by hospital treatment who are unable to pay for such care and treatment, and for pregnant women unable to pay for such care and treatment and for the children of such pregnant women born during the period of hospital care, and providing for the expense thereof, and prescribing the jurisdiction of the probate court in said cases. This law also has been found beneficial to the people of the state at large. Recently the State of Iowa has in sum and substance copied these laws, and still more recently this has been done in the State of Wisconsin. Most of the state universities in the Northwest and in the West have their medical schools and so far as we know they are liberally supported by their respective legislatures. This indicates an appreciation of medical education on the part of the public that is highly gratifying. Very recently the Legislature of Wisconsin in special session has appropriated, as we understand, more than $1,000,000 for a state hospital, and has provided for the development of a four-year medical school at Madison. The splendid work already done in that institution in the two-year course justifies this enlargement. We hope that the appreciation of state medicine

will continue to grow and that the time will soon come when every community will have its hospital where all classes of people may be examined by experts in the different lines of medicine and surgery and from which health work will radiate throughout the country. The State of Illinois has made an appropriation for its medical school and, as we understand it, the university authorities have already planned large developments, including ample hospitals, laboratories, and equipment.

In former centuries universities were founded for the most part for the purpose of teaching some religious dogma or creed. We had not only Protestant and Catholic universities, but the former were divided among Unitarians, Congregationalists, Presbyterians, and so on *ad infinitum*. Some universities have been built and endowed for the purpose of perpetuating the name of some wealthy man. All of these purposes have been laudable and have been much to the benefit of mankind at large. State universities, however, are built and supported by the people and for the purpose of making better citizens. It is not a function of the state university to admit feeble-minded or the vicious, or even to coddle its students. The state makes provision elsewhere for those of these classes. The purpose of a state university is not to make shyster lawyers or quack doctors, nor is it its purpose to enable men and women to make an easy living. The sole justification for the existence and continuance of state universities is that they provide a better citizenship. When the ordinance of 1787, providing for the territory of the Northwest, was written, its framers expressed one of their purposes in the following statement: "Religion, knowledge and morality being necessary to good government and to the happiness of mankind, schools and the means of education shall forever be encouraged." The country for which provision was then being made was at the time for the most part a wilderness of primeval forests and unbroken prairies. It has since become the very heart and core of the nation and is now appropriately called "the valley of democracy." It is pleasing to think that the spirit of the framers of the ordinance of 1787 has never perished, but has been and still is with us. The time has come for us to write into a new ordinance: there shall be no physical suffering among our people, which human skill can relieve, allowed to go unrelieved. Descartes said centuries ago, in sum and substance, that if man is ever brought to the highest possible degree of physical, mental, and moral perfection it must be through the agency of preventive and curative medicine. There is no better index to the intelligence of a people than the attention which is given to the relief of suffering among its people.

We now turn to the equally gratifying evidences of the appreciation of medical education shown by wealthy men. Mr. Rockefeller continues to give from his boundless millions for the support of medical education, and he has given wisely. During the past few months several millions have been distributed among the medical schools in this country and in Canada. The latest thing that has been done by the Rockefeller Foundation, aided by Mr. Eastman, is the very liberal provision made for a medical school in connection with the University of Rochester. This is an old institution and one which has made a highly honorable record, and we rejoice greatly that it is now to be supplied with ample provision for a medical school. Medical education is costly and there are none too many good medical schools in this country; and what is more gratifying than anything

else is that practically all these schools are good ones. It is often said that we have too many physicians already in this country. Some one figures out that we have about one doctor for every seven or eight hundred inhabitants, and calls attention to the fact that no such abundance of doctors exists in any of the European countries. If medicine is going to reap its richest rewards, and it can do this only by rendering its greatest service, there must be more skilled physicians than there are at present. One doctor to eight hundred persons convinces most of us that there are already too many physicians. Probably there are, under the system of practice now in vogue, but if state medicine is to come, and we would be loath to think it possible for it to fail to come, we shall need many times the number of physicians we now have. The army regulations provide for seven medical officers for every one thousand enlisted men and the enlisted medical corps is ten per cent of the force. It is a safe estimate to say that among 100,000,000 people the number of those daily sick is not less than 3,000,000. We shall leave it for some one else to compute how many doctors and nurses would be necessary to give the best attention to these people. The army regulations provide that hospital beds shall number not less than five per cent of the strength of the command. There will probably never be so large a demand for hospital beds among civilian populations, but the number now in existence will need to be multiplied many times.

Besides attending to the physical needs of the people, medical research must be provided for more abundantly in the future than is done at present. We know but little as yet concerning the diseases that most commonly afflict us. What do we know about measles? How much have we done to restrict this disease? What is its cause? How much is the death rate in this disease affected by secondary infections? What can we say about the accuracy of any morbidity statistics that we have pertaining to this disease? What is the average death rate in uncomplicated measles? What is the death rate in measles complicated with pneumonia? Are there epidemic waves of measles, and if so, what do we know about the periodicity of these waves? What can we do to forestall or to modify an epidemic of this disease? These are simply samples of the innumerable illustrations that might be employed to show the depth of ignorance in which we still find ourselves so far as knowledge of one of the most common of the communicable diseases of infancy and childhood is concerned.

In expressing our high appreciation of the financial support now being given to medical education in this country, let us not forget that this appreciation will grow greater or smaller according to the service rendered by the profession to the well being and development of the people. While we are happy that the people at large, as represented by state and municipal governments, and great individual philanthropists, are bestowing upon the profession their favors with a liberal hand, let us see to it that the profession justifies this confidence.

—V. C. V.

The Spontaneous Disappearance of Yellow Fever from Certain Localities

CARTER[1] says that yellow fever has spontaneously disappeared from certain small ports in the West Indies, South and Central America. He says that for the spread of yellow fever in a community the following three factors are needed: (1) The presence of a person or persons in the early stages of a yellow fever attack, (2) a sufficient number of active stegomyia, (3) the presence of susceptible persons. These factors must be operative at the same time. The stegomyia acquires the infection by biting a patient in the early stages of the disease. This mosquito must then transmit the virus to a nonimmune. If there are no susceptible persons the disease dies out for want of soil in which to grow. Susceptibles must be not only present, but must be present under certain conditions of time and place with relation to mosquitoes infected from other persons with the disease. If in a given community there are no susceptible persons complying with these conditions yellow fever will disappear; in other words, yellow fever will disappear as soon as the already infected mosquitoes die. It follows, therefore, that the immigration of susceptible material to yellow fever localities is necessary for the continuance of the disease. The ports which have been spontaneously freed from this disease receive little or no immigration of susceptible persons. It has been observed that other localities have suffered less and less from yellow fever as their prosperity declined and the arrival of traders and others decreased. The decline of the sugar industry in some of the West Indian Islands has led to this result. The withdrawal of European garrisons and fleets from the endemic area of yellow fever has resulted similarly. Even the War has helped to stamp out yellow fever on account of the commercial depression felt most keenly in certain small places in the endemic area. Carter believes that in time yellow fever may be entirely exterminated. He says that many of the higher forms of life have permanently disappeared from the earth, some of them even in our own times. He thinks this might be made an international basis for the extermination of a virus which has proved itself so pathogenic to man and which in the past has taken heavy toll of human life.

—*V. C. V.*

Fatal Anaphylaxis Following the Prophylactic Administration of Antitetanic Serum

GURD and Roberts[2] report the case of a soldier who, a few hours previously had received several small bomb wounds on both hands, the right thigh, and the left calf. All wounds were in and of themselves unimportant and the patient was apparently in good condition, being a well built man of about thirty years of age, with normal pulse and temperature. Inasmuch as the soldier had not received antitetanic serum before being wounded, he was given at 11:15 A.M. 5 c.c. of antitetanic serum subcutaneously over the right pectoralis major muscle.

[1]Ann. Trop. Med. & Parasitology, xiii, 4.
[2]The Lancet, London, April 3, 1920.

There was no disturbance until 1:30, when the soldier began to vomit and had a bloody diarrhea. Between 1:30 and 5 P.M. he vomited eight times and had six bowel movements. At the last-mentioned hour his pulse was 104 and his temperature 102.8°. The collapse continued during the night and at 6 A.M. on the next day the pulse was feeble and the beat 180. Death resulted at 10:30 A.M. on that day. The authors state:

"In so far as we are able to discover, the patient had not been previously wounded, nor had he received at any other time injections of horse serum. That he was an individual presenting a natural hypersensitiveness to horse serum is therefore a fair assumption. The fact that the same person is not infrequently sensitive to more than one foreign protein in all probability offers an explanation of the patient's history of repeated attacks of vomiting and bloody diarrhea. * * * That symptoms of respiratory spasm were not noted clinically is explained in part by the fact that, owing to pressure of work, the patient was not under constant supervision, and, more particularly, because the splanchnic reaction was predominant and so weakened the patient that expiratory dyspnea was not sufficiently evident to be noted by the sister in charge of the case. Deficient oxygenation of the tissues during life was evidenced by the extreme degree of cyanosis. It is now definitely established that man reacts to anaphylactic shock in one or other or both of two ways, in addition to the well-known cutaneous phenomena. Either he reacts in the manner which characterizes the phenomenon in the dog; i.e., splanchnic dilatation, drop in blood pressure, cardiac failure, and death—or in the way in which the typical reaction occurs in the guinea pig; i.e., bronchiole spasm, expiratory dyspnea, and death from arrest of respiration."

This case illustrates the necessity of giving first a minute dose of serum of any kind whenever administered.

—*V. C. V.*

The Diagnosis of Malaria

O'CONNELL[1] calls attention to the frequent want of harmony between the clinical and microscopic diagnosis of malaria. He mentions three cases diagnosed clinically as sunstroke but which were found by microscopic examination to have been malignant malaria; five cases of dysentery were found to be malarial enteritis; cases diagnosed clinically as relapsing and typhus fevers were shown to be malaria with relapses; cases believed at first to be influenza, on account of the prevalence of that disease, were subsequently shown to be malignant malaria. On the other hand, in Palestine, malaria is highly prevalent and here the microscope upsets all ideas of clinical experience. Parasites are found swarming in the blood of some, especially children, who exhibit no rise of temperature, and who are to all appearances in good health, whilst another suffering from what is clinically a typical malarial fever, not even one parasite can be found in the blood. Consequently, it is possible that the subsequent discovery of parasites in a patient's blood does not mean that the original clinical diagnosis of another disease must necessarily have been an error. Furthermore, failure to find parasites in the

[1]The Lancet, London, February 28, 1920.

blood during the first days of a primary attack of malaria does not exclude the possibility of the disease being malaria. The absence of parasites from the blood during the first few days of a primary attack of malaria was doubtless the reason that there were some who, when Laveran announced he had discovered parasites in malarial blood which were the cause of the fever, asserted that the bodies he discovered were not parasites but pseudoparasites. Their late appearance in the blood was given as a reason for regarding them as an effect and not the cause of the fever.

—*V. C. V.*

Tuberculosis Research Fellowship, University of Minnesota

TO encourage study of the means for the prevention and cure of tuberculosis, the Hennepin County Tuberculosis Association of Minneapolis, Minn., announces that it has set aside a fund for the support of a tuberculosis research fellowship in the Graduate School of the University of Minnesota. The candidate for the fellowship must be a graduate of a Class A medical college. He will be expected to devote himself to research in some problem concerned with the causes, prevention, or cure of tuberculosis. No teaching or other service will be required. The fellowship yields $750 the first year and progressively increasing amounts to be appropriated for the second and third years as conditions warrant. Inquiries and requests for application blanks should be addressed to the Dean of the Graduate College, University of Minnesota, Minneapolis, Minn.

United States Training Corps for the Promotion of the Health of Women

THE United States Training Corps for Women is an organization incorporated under the laws of the State of Illinois not for pecuniary profit. From its inception the purpose of the organization met with the warmest commendation and support from official Washington and the leaders of constructive thought and action.

The organization had its origin in the necessity for conducted physical exercise brought about by the crowded office and housing conditions in Washington during the war, when many women were summoned to Washington to fill government positions vacated by men called to the colors. Thirty-five hundred office women were organized into thirty companies, or three regiments. They were given military drill, taught to stand erect, to breathe properly, and were given practical talks on health, hygiene, and sensible dress. The result in health and efficiency was so marked that it commanded the attention of the heads of the departments of the government, and at their suggestion and advice, the United States Training Corps was organized November 22, 1918.

A bill is at present pending to authorize the Secretary of War to grant the

use of land and camp equipment to the United States Training Corps, and to detail army officers for service at recreational camps. When this bill passes, plans have been made for the establishment of five large recreational health camps for women to be located in the East, in the Southeast, in the West, in the Middle-West, and in the South. It is also planned to locate camps outside large industrial centers where women employees may live during the summer and go to and from their work. They will be under the direction of trained military leaders who will give the military drill and setting-up exercises adapted to women.

The first camp was conducted during the month of August, 1919, at Lake Geneva, Wisconsin, and proved to be a success. Camp No. 2 for 1920, will be held at Asheville, N. C., July 15, to August 25. The site selected is on a beautiful wooded knoll across the Country Club from the Grove Park Inn, commanding a wonderful view of the Asheville valley. While the spot is secluded and well adapted to the development of camp morale, it is within easy access of the train.

The purpose of the organization is to promote the health, efficiency and happiness of society, professional, home, and business women, and to send them home physically and mentally fit. Setting-up exercises for children in the public schools and in parks will also be emphasized. Any woman, twenty years of age or over, is eligible for membership, provided she brings a certificate from her physician stating that she has no communicable disease and is physically able to take exercise.